ANNALS of ALLERGY

Published by
The American College of Allergists

Volume 9 November-December, 1951 Number 6

PULMONARY DISTRIBUTION OF RADIOACTIVE PARTICLES IN RABBITS AFTER INHALATION AND INTRAVENOUS INJECTION

GEORGE V. TAPLIN, M.D., JAMES S. GREVIOR, M.D., MARY LOUISE GAUTSCHI, B. A., CAMILLE FINNEGAN, B.A., and ARTHUR DUNN, M.A.

West Los Angeles, California

IN a previous report, the pulmonary distribution of barium sulfate dust and *Bacillus subtilis* spores administered to rabbits by inhalation and intratracheal insufflation has been described.[25] It was shown by microscopic techniques that particles of barium sulfate 2 to 3μ or less penetrated to the alveoli, whereas particles 5 to 10μ or less were demonstrated in the trachea and large bronchi. Also, *B. subtilis* spores (0.5 to 1.5μ) were seen throughout the entire tracheobronchial tree and alveoli. Further evidence of the deep penetration of inhaled particles has been obtained with penicillin dust in similar rabbit and mouse experiments and in man.[8] In these studies it was readily shown that all the parts of the lungs contained high concentrations of penicillin. The penicillin values in lung tissues were significantly higher than the blood levels obtained simultaneously, indicating that the penicillin had reached the lung via the bronchial route, rather than via the blood stream. However, all of these data were necessarily qualitative, because of technical difficulties.

An accurate knowledge of the pulmonary retention and absorption of aerosols is needed, because various therapeutic agents are being administered as dusts or as mist type aerosols.[1,7,18-20,22-24,27-28,31] Also, more exact information of this kind is required in industrial medicine.[3,11,14-15,30] Further, in case of atomic warfare, the hazards of inhaling radioactive dusts or mists pose some very difficult problems.[9-10,13]

In all inhalation studies the problem of particle size has plagued most investigators. It is next to impossible to produce a dust which is composed of fine particles in a narrow range of size distribution and which at the

This article is based on work performed under Contract No. AT-04-1-GEN-12 between the Atomic Energy Commission and the University of California at Los Angeles.

Approved for publication August 2, 1951.

same time is free of aggregations due either to electrostatic effects or moisture. Wet aerosols show less agglomeration, but the commercial nebulizers actually produce a very wide size distribution of droplets when one includes the "rain."[1] These large particles may be removed by use of baffles or by passing the aerosol through coils of tubing. However, the length of life of a 1μ drop of water is extremely short due to evaporation,[2] and variations in temperature and humidity alter particle sizes of wet aerosols. The same is true of dusts. Thus, it is apparent that quantitative measurements are difficult to obtain in ordinary inhalation studies with aerosols in general.

Previously we described the preparation and use of *B. subtilis* spores by inhalation.[25] *B. subtilis* spores have an ideal size range (0.5 to 1.5μ) for pulmonary penetration studies. The greatest difficulty encountered in determining the pulmonary distribution of these organisms is their identification, microscopically. Thus, it was decided to turn to radioactive techniques, by which the spores could be tagged with P^{32} and their distribution in the lungs detected by measuring beta activity. In this way the amount of radioactivity in various parts of the trachea and lungs may be determined with a high degree of accuracy, and the method presents an accurate estimate of the amount and number of particles retained. By sacrificing animals at increasing intervals after exposure, the values for beta activity indicate the relative rates of removal or absorption from the specific areas tested.

The purpose of this report is to describe the techniques used in the production of P^{32} tagged spores, the procedures and precautions employed in inhalation exposure, and finally the results of pulmonary distribution and lung clearance as determined by measuring beta activity in the separate lobes of the lung and in the tracheas of rabbits following a single short inhalation exposure to an atmosphere containing these organisms.

MATERIALS AND PROCEDURES FOR PREPARING P^{32} TAGGED B. SUBTILIS SPORES

Preparation of Synthetic Media Containing P^{32}.—To promote a high degree of P^{32} uptake by the bacteria, a special synthetic medium containing a minimum amount of stable phosphate is prepared. Stock solutions of each of the following constituents are made separately:

(a)	Na Citrate	4.23 gm/100 ml
	$MgSO_4$	0.004 gm/100 ml
(b)		
	NH_4Cl	.793 gm/100 ml
(c)	KH_2PO_4	1.75 gm/100 ml
	Dextrose	40.00 gm/100 ml
(d)		
	Asparagin	1.00 gm/100 ml

The synthetic solid medium is made by combining the stock solutions in the following proportions:

Na Citrate	50.00 ml
$MgSO_4$-NH_4Cl	48.00 ml
KH_2PO_4	0.25 ml
Agar (bacto)	1.00 gm

Carrier-free radioactive phosphate solutions, containing 0.5 mc in 0.75 ml, is added and the mixture is transferred to Petroff culture flasks, using sterile technique. The medium is sterilized by autoclaving and is cooled to 48° C. Then 0.5 ml of the sterile dextrose asparagin solution is added. Finally the flasks are slanted and the medium is allowed to harden.

Preparation of P^{32} Tagged B. subtilis Spores.—The radioactive slants are inoculated by flooding the agar surface with 1 ml of an aqueous suspension of *B. subtilis* bacilli. The slants are then incubated at 30 to 34° C. for eight to ten days or until sporulation occurs. The tagged spores are harvested by flooding the slants with saline or distilled water, followed by scraping the spores from the agar surface with a glass rod. The spore suspension is centrifuged at low speed (1,000 rpm) for ten minutes to remove bacterial forms. The supernatant suspension is then washed repeatedly by centrifuging at high speed (5,000 rpm) and decanting until the supernatant saline is free of radioactivity.

To prevent germination, the tagged spore suspension is transferred to a flask containing sterile glass beads, shaken to break up aggregates, and killed by immersion in an 80° C. water bath for one hour. This stock suspension is kept refrigerated at 5° C. and standardized regarding beta activity per ml.

INHALATION PROCEDURES AND EQUIPMENT

General Principles and Radiological Safety Features.—Prior to performing inhalation experiments with radioactive materials, several dry runs are made, simulating all the conditions to be encountered later. Then pilot studies are performed, using low activity suspensions. These preliminary exercises are necessary and helpful in discovering and correcting potentially dangerous features in the procedure. The laboratory is cleaned, benches and tables are covered with paper, and the inhalation apparatus and accessory equipment are assembled. Personnel are instructed to wear rubber gloves and filter type masks during the entire experimental period. During development of the procedures, it is essential to monitor the room air and the equipment and personnel almost continuously to discover leaks in the apparatus or faulty technique. At the end of each experiment, the apparatus is cleaned, liquid wastes are diluted, and the animal carcass is incinerated. The laboratory and personnel are again monitored.

Inhalation Chamber and Accessory Equipment.—The apparatus and equipment used for exposing rabbits singly to an atmosphere containing aerosolized P^{32} tagged *B. subtilis* spores is shown in Figure 1. Essentially, it consists of an inner boot-shaped exposure chamber and a rabbit restraining box, enclosed in a larger plastic rectangular container plus a nebulizer.

The double chamber arrangement is designed to prevent contamination of the room air, by permitting evacuation of the outer chamber through a filtering apparatus (vacuum cleaner type). The nebulizer is operated by compressed air and aerosolizes 3 ml of the tagged spore suspension in about thirty minutes when the flow rate is regulated at 7 liter/minute. The suspended particles are directed into the toe of the boot chamber, pass by the animal's head, and leave through an outlet in the heel of the boot. This opening is connected to a simple filtering device which permits the circulation of air but retains the suspended particles.

Methods for Determining Beta Activity in Tissue Specimens.—Animals are sacrificed by intravenous air injection. Autopsies are performed using aseptic technique. Weights of the lobes of the lung and trachea are measured so that radioactivity may be calculated per gram (wet weight) of tissue. Specimens of tissue are prepared for counting by mincing and by digestion with 6 $NHNO_3$, followed by homogenization. Aliquot samples are distributed evenly over the bottoms of stainless steel counting caps dried at 110 to 130° C. and then ashed in a muffle furnace at 500° C.

The ashed samples are counted, using a Potter scaler, for at least 2,000 counts or more if indicated. Background levels are determined twice daily during the experimental period. The values for daily background have been fairly constant, and the accumulative background during the period of the experiment was approximately 0.3 c/s.

The geometry of the counter is determined by use of the primary standards, UX, UX_2 + $Cs137_B$– and is 8.65 per cent in shelf No. 1. The rate of decay in each spore suspension used is determined by plotting the activity in aliquot samples at one to two day intervals, for the duration of the experiment.

The beta activity in all samples is reported in disintegrations per second, plus or minus the Standard Error, corrected for decay. The Standard Error is computed using Jarret's formula:[17]

$$Q = K\sqrt{\frac{Ns}{Ts} + \frac{Nb}{Tb}}$$

K=1 (For Standard Error)
Ns=Counts/sec. for sample and background
Ts=Time in seconds to count sample and background
Nb=Counts/sec. for background
Tb=Time in seconds to count background
Q=Error in counts/sec. for sample being counted.

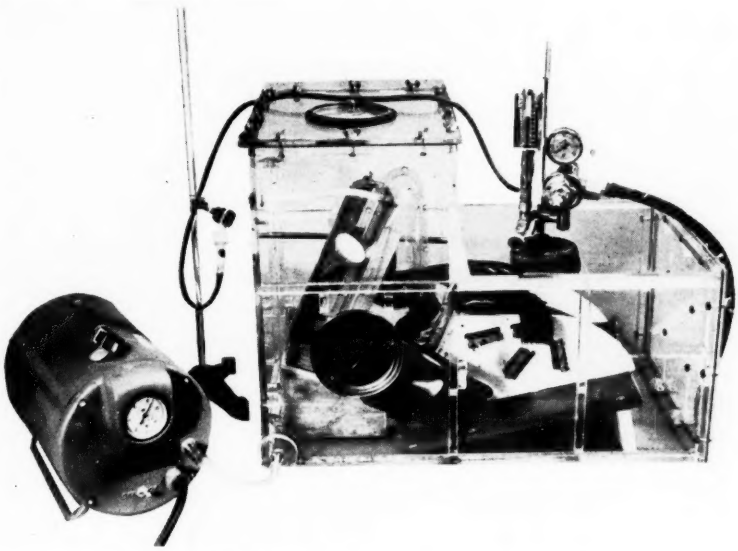

Fig. 1. Inhalation apparatus and accessory equipment.

PRELIMINARY STUDIES

Initial inhalation experiments were performed using spore suspensions with low P^{32} content (0.6 to 2.0μc/cc). Results showed that complete pulmonary penetration had occurred. Each of the lobes of the lungs and the tracheas had values for beta activity well over background.

PULMONARY DISTRIBUTION AND LUNG CLEARANCE STUDIES

Subsequently, similar experiments were conducted, exposing rabbits for single thirty-minute periods to nebulized P^{32} tagged *B. subtilis* spores with somewhat higher beta activity. In these studies, beta activity in tissue specimens was determined per gram of tissue, and reported in d/s (disintegration/second) corrected for decay. By exposing a series of rabbits under conditions as nearly identical as possible, and by sacrificing them after increasing intervals, one may estimate the rate and degree of clearance of inhaled particles from the respiratory tract, in addition to determining the distribution of such material in the pulmonary tree. The data presented in Figure 2 show that tagged spores are cleared from the trachea in one to two hours but remain in the lung parenchyma for at least seventy-two hours. The values for beta activity recorded at each time interval represent the average of two or three separate experiments. The activity remaining in lung tissue at seventy-two hours probably represents spores that have penetrated beyond the area where the respiratory lining membrane is

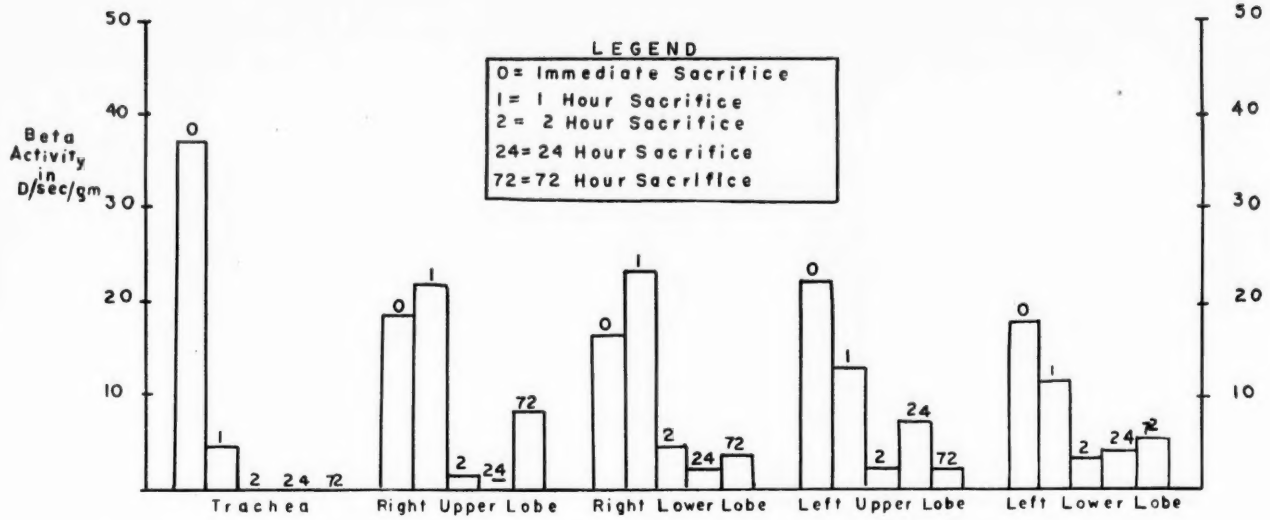

Fig. 2. Distribution of P^{32} tagged *B. subtilis* spores in the respiratory tract of rabbits and their clearance at various intervals after a thirty-minute inhalation exposure. Notes: Identical determinations were made in three rabbits exposed to nonradioactive spores in the same manner. Control values were not significantly above background in any instance. Standard Error in counting varied between 2 and 6 per cent.

TABLE I. DISTRIBUTION OF P^{32} TAGGED *B. subtilis* SPORES IN ORGANS OF THE RETICULOENDOTHELIAL SYSTEM FIFTEEN MINUTES AFTER INTRAVENOUS INJECTION

Sample	Wet Weight of Tissue (grams)	c/s/gram above background	Disintegrations/ sec. per gm of tissue		Per cent Recovery
Blood, control	1.00	.08	....	..	....
Blood, 5 minutes	1.00	1.85	22.62±	.16	....
Blood, 10 minutes	1.00	1.02	15.06±	.10	....
Lung	9.40	3.17	46.75±	.19	2.98
Liver	46.15	10.08	148.40±	.13	46.15
Brain	7.43	.09	....	..	....
Kidney	6.19	.34	4.99±	.08	.19
Spleen	1.13	56.82	812.00±	.37	6.22
Bone Marrow	.79	2.78	39.70±	.15	.21
				Total Recovery	55.75

1. Dosage: 3 ml containing .13 μc (4,919 d/s) per ml
2. Background: 0.299 c/s
3. Geometry: 8.93%
4. d/s per gram are corrected for decay, and are shown with the Standard Error in counting

TABLE II. DISTRIBUTION OF P^{32} IN ORGANS OF THE RETICULOENDOTHELIAL SYSTEM FIFTEEN MINUTES AFTER THE INTRAVENOUS INJECTION OF THE ISOTOPE SOLUTION

Sample	Wet Weight of Tissue (grams)	c/s/gram above background	Disintegrations sec. per gm of tissue		Per cent Recovery
Blood, control	1.00	.094	....	..	....
Blood, 5 minutes	1.00	6.77	149.72±	.34	....
Blood, 10 minutes	1.00	4.62	102.16±	.28	....
Blood, 15 minutes	1.00	3.03	66.88±	.15	....
Lung	8.48	3.02	66.12±	.18	.74
Liver	73.86	2.73	70.00±	.20	5.91
Brain	6.55	.30	6.45±	.08	.05
Kidney	7.19	5.37	133.07±	.33	10.79
Spleen	1.11	1.16	28.75±	.13	.03
Bone Marrow	.79	4.96	122.79±	.19	.11
				Total Recovery	17.63

1. Dosage: 3 ml containing .81μc (29,834 d/s) per ml
2. Background: 0.296 c/s
3. Geometry: 8.80%
4. d/s per gram are corrected for decay, and are shown with the Standard Error in counting

ciliated. Attempts have been made to prove the point by radioautography. However, so far, it has not been possible to prepare thin sections containing sufficient beta activity to produce satisfactory autoradiographs.

DISTRIBUTION OF P^{32} IN THE LUNGS AND OTHER ORGANS OF THE RETICULOENDOTHELIAL SYSTEM AFTER ADMINISTRATION IN DIFFERENT FORMS AND BY OTHER ROUTES

It became apparent that pulmonary distribution data would have more significance if similar information were obtained following intravenous injection of the tagged spore suspension and after inhalation exposure of the animals to a nebulized mist of the isotope solution.

The distribution of P^{32} tagged *B. subtilis* spores in the lungs and other organs of the reticuloendothelial system fifteen minutes after an intravenous injection is shown in Table I. Results of a similar experiment following intravenous injection of the isotope solution are presented in Table II.

TABLE III. DISTRIBUTION OF P^{32} IN THE RESPIRATORY TRACT AFTER A 30-MINUTE INHALATION EXPOSURE TO A NEBULIZED MIST OF THE ISOTOPE SOLUTION

Sample	Wet Weight of Tissue (gram)	c/s/gram above background	Disintegration/ sec. per gm of tissue
	Immediately		
Trachea	1.00	1.31	24.78 ± .17
Right Upper Lobe	1.92	.20	3.70 ± .10
Right Lower Lobe	2.97	.23	4.26 ± .13
Left Upper Lobe	.99	.27	5.05 ± .15
Left Lower Lobe	2.15	.14	2.79 ± .17
	Four Hours		
Trachea	1.27	.20	3.07 ± .11
Right Upper Lobe	3.20	.36	5.45 ± .13
Right Lower Lobe	2.02	.41	6.45 ± .13
Left Upper Lobe	2.16	.42	6.76 ± .11
Left Lower Lobe	1.50	.13	2.10 ± .12
	Twenty-four Hours		
Trachea	1.56	.43	6.48 ± .12
Right Upper Lobe	1.19	.30	4.55 ± .11
Right Lober Lobe	2.02	.37	5.50 ± .12
Left Upper Lobe	2.21	.28	4.15 ± .12
Left Lower Lobe	1.55	.30	4.66 ± .13

1. Dosage: 3 ml containing .81μc (29,834 d/s) per ml
2. Background: 0.296 c/s
3. Geometry: 8.80%
4. d/s per gram are corrected for decay and are shown with the Standard Error in counting

By comparing the per cent recovery of P^{32} in each of the various organs, it is seen that when the P^{32} is incorporated in the spores, the isotope is localized in high concentration in the lung, liver, and spleen, whereas after intravenous injection of the isotope solution, the beta activity is highest in the kidneys and liver and is relatively low in the lung and spleen. This characteristic difference in distribution pattern between solutions and particulate suspensions verifies the effectiveness of the tagging procedure and also demonstrates that 1μ-sized particles are removed from the circulation mainly by the liver.

Two additional series of experiments were performed to provide further proof that our spore suspensions were effectively tagged and that their distribution in the trachea and lung has a relationship characteristic of the method of their administration. First, three rabbits were given a thirty-minute inhalation exposure to a nebulized mist of the isotope solution. One was sacrificed immediately, and the other two were killed after four- and twenty-four hour intervals. From Table III it is seen that the beta activity is relatively high in the trachea compared with lung values immediately after exposure, but this value falls within four hours to one about the same as the activity in the various lobes of the lung. These findings are similar to our results where the rabbits were exposed to atmospheres containing the P^{32} tagged spores.

By contrast, when rabbits are given an intravenous injection of the tagged spores suspension, the distribution of P^{32} in the trachea and lung is different. In Table IV it is seen that the beta activity in the trachea at the

TABLE IV. DISTRIBUTION OF P^{32} TAGGED *B. subtilis* SPORES IN THE RESPIRATORY TRACT AFTER INTRAVENOUS INJECTION

Sample	Wet Weight of Tissue (grams)	c/s/gram above background	Disintegrations sec. per gram of tissue
	Immediately		
Trachea	1.06	.41	6.05 ± .34
Right Upper Lobe	2.84	2.74	41.27 ± .18
Right Lower Lobe	2.71	2.68	39.47 ± .16
Left Upper Lobe	2.41	3.68	55.43 ± .56
Left Lower Lobe	1.04	3.59	52.91 ± .26
	Four Hours		
Trachea	.98	.15	2.13 ± .11
Right Upper Lobe	1.61	1.17	15.57 ± .15
Right Lower Lobe	1.61	1.13	15.06 ± .15
Left Upper Lobe	1.55	1.27	16.97 ± .12
Left Lower Lobe	.62	1.14	15.23 ± .12
	Twenty-four Hours		
Trachea	.62	.21	2.80 ± .11
Right Upper Lobe	1.93	2.68	32.87 ± .66
Right Lower Lobe	2.35	1.46	17.86 ± .15
Left Upper Lobe	1.78	2.86	35.44 ± .22
Left Lower Lobe	.76	...	.... ..

1. Dosage: 3 ml containing .13μc (4,919 d/s) per 1 ml
2. Background: 0.299 c/s
3. Geometry: 8.93%
4. d/s per gram are corrected for decay, and are shown with the Standard Error in counting

same intervals after injection is always relatively low compared with that of lung tissue.

These studies demonstrate that P^{32} tagged *B. subtilis* spores are deposited and retained in the trachea and lungs of rabbits in a distinctly different relationship after inhalation compared with intravenous injection. The inhalation pattern is characterized by relatively high tracheal values compared with those in the lung. The distribution pattern after intravenous injection is characterized by low tracheal and high lung values. Further, there are differences in clearance from the respiratory tract. After inhalation the trachea is cleared rapidly, whereas after injection there are no significant changes in the trachea during the first twenty-four hours. The pulmonary parenchyma is relatively slowly cleared after both modes of administration, although the mechanisms are not the same.

DISCUSSION AND INTERPRETATION OF RESULTS

In evaluating the potential hazard from inhaling fission products following a contaminating atomic explosion or from exposure to noxious dusts or smokes in industry, there are many factors to be considered. The important factors may be listed as follows:

1. Particle size of the material and depth of pulmonary penetration.
2. Amount retained in the lungs.
3. Solubility and absorbability of the agents from the respiratory membranes.
4. Density of the material.

5. Duration of exposure.
6. Toxicity of the substance in its nonradioactive form.
7. Physiological mechanisms for its absorption, retention, or clearance from the respiratory tract.
8. Redistribution in the body of materials absorbed through the respiratory tree and gastrointestinal tract.

It has been demonstrated by others[14-15,30] that particle size is a major factor in determining the depth of pulmonary penetration. In general, only particles smaller than about 5μ reach the alveoli; larger-sized particles are deposited in the upper respiratory passages.[14,30] Also, as the particle size is decreased below 1μ, less is retained in the lung parenchyma, because more is lost during exhalation.[15] Further, the ciliated epithelium of the respiratory tract has been shown to be highly efficient in removing foreign material from the bronchial passages.[4-6,12,16,21,29] However, insoluble material penetrating beyond the bronchioles is retained for prolonged periods.[13]

Thus, with radioactive material the greatest damage from radiation injury to the lung probably would be to the alveolar areas, or at odd sites where the material might be localized because of mechanical or pathological factors. Much of the material removed from the respiratory passages by ciliary action eventually reaches the intestinal tract and is eliminated or partly absorbed.

From these considerations, it is apparent that the inhalation of insoluble radioactive particles having a mean size range of about 1μ is potentially dangerous.

Our pulmonary distribution and lung clearance studies with P^{32} tagged spores indicate that a single short inhalation exposure to an atmosphere composed entirely of insoluble particles about 1 μ in size results in immediate contamination of the entire respiratory tract. However, in rabbits, the trachea and presumably the bronchi clear themselves within a few hours, whereas the lung parenchyma retains a significant percentage (15 to 25 per cent) of the total amount of tagged material initially deposited for at least seventy-two hours. Similar studies are in progress to determine the maximum duration of pulmonary retention of fine particles in normal and irradiated rabbits.

SUMMARY

Inhalation studies in rabbits using radioactive particles of uniform size distribution (P^{32} tagged *B. subtilis* spores) indicate that insoluble fine particles (0.5 to 1.5 μ) are distributed evenly throughout the lobes of the lung and trachea immediately after a thirty-minute inhalation exposure.

By serial sacrifice techniques, it has been shown that the trachea and presumably the bronchi are cleared rapidly, whereas the lung parenchyma retains a significant amount of the material initially deposited for at least seventy-two hours. These findings demonstrate that a single short inhala-

tion exposure to insoluble radioactive particles about 1 μ in size may be hazardous. However, the normal lung clearance mechanisms are highly efficient and act within one to two hours to remove foreign material initially retained in the tracheobronchial tree of rabbits.

The distribution of P^{32} tagged spores in the respiratory tract and other organs of the reticuloendothelial system following intravenous injection has a pattern entirely different from that following inhalation exposure. Also, the respiratory tract clearance following injection differs from that after inhalation exposure, indicating that separate mechanisms are involved. Ciliary activity probably plays the major role following inhalation, and phagocytosis is the most likely mechanism following intravenous injection.

REFERENCES

1. Abramson, H. A.: Principles and practice of aerosol therapy of lungs and bronchi. Ann. Allergy, 4:440, 1946.
2. Abramson, H. A., and Demerec, M.: Method for experimental control of particle size of therapeutic aerosols. J. Allergy, 16:184-187, 1945.
3. Bain, G. P.; Sloan, J. Q., and Brucer, M.: Depth of penetration of nebulized substances in the respiratory tree. Federation Proc., 6:1, 1947.
4. Ballenger, J. J.: A study of ciliary activity in the respiratory tract of animals. Ann. Otol., Rhin., & Laryng., 58:351, 1949.
5. Ballenger, J. J.: The production of negative pressures by respiratory cilia. Ann. Otol., Rhin., & Laryng., 59:694, 1950.
6. Barclay, A. E., and Franklin, K. J.: The rate of excretion of India ink injected into the lungs. J. Physiol., 90:482, 1937.
7. Bryson, V.; Sansome, E., and Laskin, S.: Aerosolization of penicillin solutions. Science, 100:33, 1944.
8. Cohen, S. H.; Taplin, G. V., and Mahoney, E. B.: Inhalation of micropowdered penicillin and streptomycin in the prevention of postoperative pulmonary infection. Surgery, 24:393-400, 1948.
9. Cohn, W. E.: Toxicity of inhaled or ingested radioactive products. Nucleonics, 3:1, 1948.
10. Copp, D. H.; Axelrod, D. J., and Hamilton, J. W.: The deposition of radioactive metals in bone as a potential health hazard. Am. J. Roentgenol., 58:1, 1947.
11. Drinker, P., and Hatch, T.: Industrial Dust. Chapters I, III, and IV. New York: McGraw-Hill, 1936.
12. Gray, J.: Ciliary Movement. London: Cambridge University Press, 1928.
13. Hamilton, J. W.: The metabolism of radioactive elements created by nuclear fission. New England J. Med., 240:22, 1949.
14. Hatch, T. F., and Hemeon, W. C. L.: Influence of particle size in dust exposure. J. Indust. Hyg. & Toxicol., 30:172, 1940.
15. Hatch, T. F., and Kindsvatter, V. H.: Lung retention of quartz dust smaller than one-half micron. J. Indust. Hyg. & Toxicol., 29:342, 1947.
16. Hilding, A. C.: Production of negative pressure in the respiratory tract by ciliary action and its relation to postoperative atelectasis. Anesthesiology, 5:225-236, 1944.
17. Jarret, A. J.: Statistical Methods Used in the Measurement of Radioactivity. Mon. P-126, June 17, 1946.
18. Krasno, L.; Karp, M.; and Rhoads, P. S.: Inhalation of penicillin dust. Science, 106:249, 1947.
19. Krasno, L.; Karp, M.; and Rhoads, P. S.: Inhalation of penicillin dust. J.A.M.A., 138:344, 1948.
20. Liedholm, K.: Inhalation of liquid aerosols. Acta med. Scandinav., Suppl., 228, 1949.
21. Lucas, A. M., and Douglas, L. C.: Principles underlying ciliary activity in the respiratory tract. Arch. Otolaryng., 21:285, 1935.
22. O'Driscol, D. T.: Treatment of lung abscess by inhalation of micropulverized penicillin. Lancet, 257:949, 1949.

(Continued on Page 726)

ALLERGY OF THE URINARY TRACT

A Critical Review of the Literature with An Analysis of 613 Cases of Urologic Disease in Relation to Allergy

SUSAN C. DEES, M.D., F.A.C.A., and EILEEN C. SIMMONS, M.D.
Durham, North Carolina

ALLERGY of the urinary tract is an uncommon and perhaps debatable entity, if one can estimate its frequency by reports in the literature and from unreported clinical impressions of allergists and urologists. In order to present this subject we have reviewed and summarized the cases of urinary allergy reported in the literature. We have also reviewed Duke Hospital case histories of several urologic conditions whose etiology is not definitely established: namely, orthostatic albuminuria, essential hematuria, enuresis, ureteral spasm, chronic nonspecific trigonitis and urethritis, and interstitial cystitis. A total of 613 records have been searched for evidence of allergy in history, physical examination, and laboratory studies to determine whether allergic factors were present and could be of significance.

One general criticism of all the reported cases of urinary allergy is that those presented by allergists are likely to have inadequate urologic study to rule out organic disease, and those patients primarily studied by urologists often lack any allergic study. The reasons for these omissions are obvious, since both allergic and urologic studies are uncomfortable and expensive for the patient, and in a paper details must often be omitted for brevity.

When a definite entity is proved, then we can admit to it patients with allergy plus infection or anatomical anomaly, just as we now recognize asthma or rhinitis complicated by infection. However, until allergy of the urinary tract is definitely established and the clinical outlines are clear, the basic picture must be confined to patients with uncomplicated allergy of this system.

The symptoms of urinary allergy, as reported, involve the lower urinary tract with irritative symptoms in the urethra and bladder and the upper urinary tract with ureteral or renal colic, hematuria, or albuminuria. These reports have been tabulated in a comparison of allergic and urologic studies (Table I).[19,27,35,62,68,72] An allergic basis for lower urinary tract symptoms has been suggested in nineteen cases. Of these, fifteen had a personal history of allergy, eleven had allergy studies, a suspected allergen was identified in sixteen, and ten were relieved of symptoms by an allergy regimen (epinephrine, diet, or desensitization). The urologic studies as

From the Department of Pediatrics and Allergy, Duke University School of Medicine, and Duke University Hospital, Durham, North Carolina.
Presented at the Graduate Instructional Course, The American College of Allergists, February 9-11, 1951, Chicago, Illinois.
Approved for publication, April 5, 1951.

TABLE I. ALLERGY OF LOWER URINARY TRACT, IRRITATIVE SYMPTOMS. SUMMARY OF CASES REPORTED IN THE LITERATURE

Ref.	Cases	Personal Allergy	Allergy Studies	Allergen	Urologic Study			Rx Results
					Urine	Cyst	X-ray	
1	1	0	0	Gin Punch	0	+	0	Epineph.
2	8	6	4	8	0	1+ 2 Ng. 1?	0	5-Elim. 3
3	6	6	6	Foods	2 E. Coli	3+ 2 Ng.	0	Epin. 5 Diet 5
4	1	1	0	0	WBC RBC Mucus	+	0	Rx? Cyst. ng. 3 days
5	2	2	1 0	Inhal. ?	WBC E's	Ng.	0	1-Epin. 1?
6	1	0	0	0	0	+	0	0
Total	19	15	11	16		13	0	

described consisted of cystoscopy in thirteen, some of which were not described in detail. Urine cultures were mentioned specifically in only two patients by Duke, and these contained *E. coli.*[19] No statement is made by any of the authors concerning studies to rule out tuberculous infection. No x-rays were reported.

Hand[30] discusses the relation of allergy to interstitial cystitis in a survey of 223 cases. He reports that thirty-three of these patients (15 per cent) also had allergic disorders. He found only nineteen patients with allergy in 223 consecutive general clinic admissions. Various other chronic disorders were present with equal frequency in the two groups. Hand considers an incidence of allergy of 15 per cent in interstitial cystitis as more than coincidental, and as one which warrants further investigation. Thomas and Wickstein,[68] in their report on urinary allergy, describe one patient with interstitial cystitis whose symptoms were aggravated by foods and who improved in six weeks after desensitization and diet were started.

Upper urinary tract symptoms of colic or spasm attributed to allergy have been described in ten patients (Table II).[2,6,35,47,70] Allergy was present in eight, although Adelsberger[2] includes three patients with abdominal pain, having positive tuberculin skin tests with tuberculous mesenteric adenitis, who apparently had pain after taking milk. Since there is no description of allergy studies or urologic studies, these patients are difficult to evaluate. Allergy tests were done in only four of the ten patients, an allergen was identified in six, and epinephrine relieved symp-

TABLE II. ALLERGY OF UPPER URINARY TRACT, WITH COLIC OR SPASM. SUMMARY OF CASES REPORTED IN THE LITERATURE

Ref.	Cases	Personal Allergy	Allergy Studies	Allergen Identified	Urologic Study* Urine	Cyst	Rx Results
1	1	Urticaria	+	Foods	WBC E's	+** Ng. 6 wks.	Epineph.
8	1	Angioedema	+	Foods	0	0	Epineph.
9	1	Urticaria	0	?Goat Milk	Mucus	+	0
10	2	Rhinitis 0	+ 0	+ 0	Ng. Ng.	Ng. Ng.	Epineph. Epineph.
11	5	1-Eczema 3-Abd. pain 1-0	+ +TBC 0	Wheat Milk 0	0 0 0	Ng. 0 0	0 0 0
Total	10	8	4	6	4	5	

*2 patients had negative x-rays.

**Biopsy bladder mucosa, mononuclear and eosinophil infiltration.

toms in four. Of the ten patients, in only two were x-rays of the genito-urinary tract specifically mentioned, and those were negative. In two other reports, the general statement "urologic studies negative" is found. In two patients cystoscopy was described as showing bladder mucosa irritation; in one, cystoscopy was negative; in two others it was presumably negative. Again, scanty information is given of urine examinations. In view of the symptoms of renal colic, none of the patients have studies reported which would conclusively rule out, for the reader, a radiolucent stone or other organic cause for obstruction. The report of Kindall,[35] in which biopsies of the bladder mucosa showed mononuclear and eosinophilic infiltration, is perhaps the most detailed investigation of case reports of urinary allergy. Eosinophiles were present in the urine. The frequency of eosinophiles in normal urine sediment has not been reported, to our knowledge; as routine urinalysis does not include staining for eosinophiles, it is quite possible that they are often overlooked.

The upper tract symptoms of hematuria, painless in most instances, probably compatible with so-called "essential hematuria," has been ascribed to allergy in eleven reported cases (Table III).[2,13,21,37,47,56,68] A personal history of allergy was present in six patients; allergy tests were done in eight; a suspected food, drug, or physical allergen was identified in all. In these reports, the urological studies are not always described in detail and one must assume that all organic cause for bleeding has been eliminated. There is no statement in many of the reports that cultures for acid-fast organisms or retrograde pyelography was done. In three of the patients, cystoscopy was described as showing blood coming only from the right

TABLE III. ALLERGY OF UPPER URINARY TRACT, WITH HEMATURIA. SUMMARY OF CASES REPORTED IN THE LITERATURE

Ref.	Cases	Personal Allergy	Allergy Studies	Allergen	Urologic Study Cyst	Urologic Study X-ray	Rx Results
12	2	Urticaria	+	Food	+	0	Diet 2 yrs.
		Eczema	0	Sun			?
11	1	+	+	Dust	0	0	Ng. 24 hrs.
13	1	0	0	TAT	+	Neg.	Well 9 yrs.
10	2	Urticaria	+	Codfish	+	Neg.	Diet
		0	0	Seasonal	0	0	0
14	1	Urticaria	Ng.	Milk	0	0	?
15	3	?	+	Codeine	Neg.	Neg.	Elim.
		?	+	Cheese	Neg.	Neg.	Diet
		?	+	Milk	Neg.	Neg.	Diet
2	1	Headache	+	Foods	+	Neg.	Diet
				Inhalants			Desens.
Total	11	6	8	11	8	6	

ureter. Thomas and Wickstein's[68] patient had bleeding from both ureters. In Rhodes'[56,57] patient, whose symptoms followed the administration of tetanus antitoxin, there was bleeding only from the right ureter. For nine years after this patient was first reported, he remained under observation, was clinically well, and had several urological examinations which were completely negative. In three cases no cystoscopic examination was described. It is probable that none of the eleven reported cases had any organic lesion responsible for the bleeding, but it is well known that bladder, ureteral, and kidney tumors may manifest themselves by isolated brief episodes of bleeding and may remain asymptomatic for considerable periods of time before major symptoms recur and the actual pathology is discovered.

We have not found any published reports of orthostatic albuminuria as a manifestation of allergy, although it is our personal impression that this condition is frequently seen in allergic children, but we are uncertain as to whether this is more than a coincidence.

Enuresis due to allergy has been reported in 100 children by Bray,[7] who obtained good results from allergic management. Ephedrine sulfate for symptomatic treatment has been used by Kittredge[36] and Rudolf.[59] Cook[14] states that "one rarely finds organic disease in enuresis." No other intensive studies except Bray's have come to our attention, although many authors allude to allergy as an accepted cause for enuresis in certain patients. This phase of urinary allergy, too, merits further study.

TABLE IV. ALLERGY OF UPPER URINARY TRACT, WITH NEPHRITIS, NEPHROSIS. SUMMARY OF CASES REPORTED IN THE LITERATURE

Ref.	Cases	Personal Allergy	Allergy Studies	Allergen identified	Urinary Symptoms	Rx Results
21	3	Urticaria	+	Foods	Clinical Nephrosis	3 yrs. nephrosis 1 yr. sl. alb., diet
		Urticaria	+	Spinach		3 yrs. well diet
		Eczema	+	Foods		2 yrs. well diet
20	36	+	?	Hg. 22	Acute Nephritis	?
			?	As 9		?
			?	Algocratine-5		?
	4	?	?	Antitoxin		1 death
	3	?	?	Bacterial Vaccine		2 improved epin.
Total	46	3*	3	46		

Tzank[69] and others describe a type of acute allergic nephritis similar to acute glomerulonephritis, but differing from it in its sudden acute onset within minutes or hours after injection or contact with heavy metals, drugs, antitoxin, or bacterial vaccine. The symptoms are usually initiated by severe lumbar pain, urticaria, asthma, and occasionally purpura. Hematuria, cylindruria, albuminuria, azotemia, anuria develop quickly. Recovery may be complete within a few days, or the episode may terminate fatally. The nephrotic syndrome has been ascribed to food allergy by Danis.[16] These two papers are summarized in Table IV. Hematuria during the course of Henoch-Schönlein purpura has been reported as due to food sensitivity in only four patients.[3,8,40] In twelve patients studied by Gairdner[26] no instance of food sensitivity was encountered, while B. hemolytic streptococcus infection preceded purpura in one half of his group. Numerous other papers on Henoch-Schönlein purpura do not mention hematuria as a symptom, or do not ascribe the disorder to any specific allergic sensitivity.[29,50] An interesting recent report by Stefanini et al[66] on the use of ACTH in anaphylactoid purpura states that while abdominal and skin symptoms improved during this therapy, urinary albumin persisted. Favism with hematuria is considered an allergic reaction to fava bean or pollen, but in only one of the five patients reported from the United States has the skin test been positive.[3,32,41,43] Paroxysmal hemoglobinuria represents an allergy to malaria protozoan products according to Fernán-Nuñez, who studied fifty-two cases in Colombia.[23] He found six-

teen positive skin tests to malaria protein in 410 persons tested. Moving these sixteen persons to other stations eliminated blackwater fever from the area. Autopsies of eleven other patients dying with blackwater fever showed eosinophilia of the tissues. No other reports of studies confirming or amplifying this work have been found.

The effects of hemoglobin and products of tissue breakdown on the kidney have been described in an excellent review by Ross,[58] in which he points out that sensitivity of the kidney to hemoglobin may be the mechanism operating in paroxysmal cold hemoglobinuria,[73] paroxysmal nocturnal hemoglobinuria, and the very rare "Haff" disease.

A complete review of the problem of cellular or tuberculin type of sensitivity of the urinary tract is beyond the scope of the present discussion.[54] Evidence accumulates to reinforce the idea that nephritis may be a sensitivity reaction in glomeruli, blood vessels, connective tissue, and tubular epithelium to tissue or bacterial products.[12,17,44,54,65] Similar reactions are seen in sensitivity to chemicals either in the course of therapeutic administration[24,67] or in experimental animals.[22,38,52] Effects of nephrotoxic sera administered to experimental animals, tagged with radioactive iodine or with colored azo-dyes,[39] have demonstrated that such preparations are found in kidney tissue in high concentrations and for considerable periods of time. Along with this have been studies of the tissue changes in such experimental animals which resemble those of acute nephritis in man.

Acute nephritis following severe ivy dermatitis has been described by Rytand[60] in seven patients, while in two others he found periarteritis nodosa[61] as a sequel to ivy dermatitis. Reiter's syndrome has been considered an allergic reaction, but recent studies indicate that a pleuropneumonia organism is present in a large number of patients.[18,51,63,64] Vaginitis, vaginal irritation on urination, and urethritis and balanitis have occasionally been considered of allergic origin.[1,9,28,45,55]

In personal communications from fourteen prominent urologists in various parts of the country ten report that they have no bona fide cases of urinary tract allergy. All of these urologists[4,15,31,34,42,46,49,71,74] state that they have often considered an allergic basis for certain cases; several feel certain that they have seen an occasional patient whose urologic symptoms were due to allergy, but the final proof was inconclusive.[15,31,74] Severe irritative bladder symptoms and urticaria due to proven peanut sensitivity in one patient were reported from one clinic,[53] while another urologist reported similar symptoms regularly occurred in one of his patients after eating asparagus.[5] One urologist had observed two women with seasonal bladder irritation whose symptoms responded only to Pyribenzamine.[15] In both there was marked trigonitis and urethritis on cystoscopy, with negative urine. In one of these women who was cystoscoped before and after Pyribenzamine "there was a phenomenal improvement in the appearance of the bladder mucosa." Another urologist[11] had

TABLE V. INCIDENCE OF ALLERGY IN 613 UROLOGIC PATIENTS, DUKE HOSPITAL

Diagnosis	Cases Reviewed	Family or Personal History		Personal History Cases	%
		Cases	%		
Orthostatic Albuminuria	82	18	22%	14	17%
Essential Hematuria	32	5	15%	5	15%
Enuresis	185	26	14%	17	9%
Spasm of ureter	14	2	15%	2	15%
Chronic Trigonitis and Urethritis	269	35	13%	30	11%
Interstitial Cystitis	31	5	16%	5	16%
Total	613	91	15%	73	12%

observed the patient with hematuria due to unboiled cow's milk reported by Kittredge and Brown.[36]

Burkland[10] has studied many patients in whom he suspected allergic reactions in the urinary tract; among them is a woman with severe irritative bladder symptoms, whose urological examination was negative except for congestion and edema of the posterior urethra and ureteral orifices at cystoscopic examination. She had a blood eosinophilia of 46 per cent. Allergy tests revealed sensitivity to walnut pollen, crab, and shrimp; with avoidance of these things plus Pyribenzamine the symptoms disappeared, and eosinophiles dropped to 6 per cent. Re-exposure to pollinating walnut trees was followed by recurrence of urinary symptoms.

Nickels[48] describes a case of bladder irritation, perineal discomfort, and deep suprapubic pressure sensation lasting two to five days in a fifty-five-year-old male whose urinary sediment contained an occasional mononuclear leukocyte and eosinophile. The prostate was boggy, and the expressed prostatic fluid contained one leukocyte per high power field. These were mainly mononuclear cells with an occasional eosinophile. One of the offending substances was found to be any alcoholic beverage. By taking ephedrine at least one hour before ingesting the offending substance, he could prevent the urinary symptoms. If no ephedrine preceded the alcoholic beverage, the reaction always occurred and ephedrine would relieve symptoms in one to two hours.

A great many allergists have been questioned regarding the incidence of allergic reactions in the urinary tract among their patients. The general consensus was that many believed they had seen such patients, but from none were we able to obtain any thoroughly studied cases other than those previously reported in the literature.

Turning now to the 613 urologic patients whose histories we have surveyed for evidence of allergy, we find allergy in other systems in 12 per cent of the group (Table V). We have selected the following conditions

for analysis: essential hematuria, orthostatic albuminuria, enuresis, ureteral spasm, chronic trigonitis, and urethritis and interstitial cystitis. These conditions most nearly resemble the disorders reported in the literature as having at times an allergic basis. The patients were all seen by members of the urologic department, by whom the urologic diagnosis was made.

TABLE VI. CRITERIA FOR DIAGNOSIS OF ORTHOSTATIC ALBUMINURIA (YOUNG, HAINES AND PRINCE)

A.	1. Absence of albumin in urine secreted in horizontal position.
	2. No past history of renal or CV disease.
	3. No elevation of blood pressure.
	4. No RBC, WBC, or casts in urine.
B.	5. Normal kidney function (PSP-urea or dilution-concentration).
	6. Normal blood chemistry (NPN, urea, total protein, A/G ratio).
C.	7. Negative flat plate of abdomen and normal I.V. urogram.

TABLE VII. INCIDENCE OF ALLERGY IN 82 PATIENTS WITH ORTHOSTATIC ALBUMINURIA

Groups	Cases	Family and Personal Allergy	% of group	Personal Allergy	% of Group
Group A	82	18	22%	14	17%
Group B	68	13	19%	10	14%
Group C	20	3	15%	3	15%

Orthostatic Albuminuria.—An analysis of eighty-two cases of orthostatic albuminuria using the criteria (Table VI) suggested by Young, Haines and Prince[75] reveals personal or family allergy in eighteen persons, or 17 per cent of the entire group (Table VII). When the allergic and urologic studies are compared, we find that major allergy was present in five patients, minor allergy in nine, all of whom were skin tested. Four patients had positive family histories but were not skin tested. Three of the patients with major allergy had both complete allergic and urologic studies. In none of these patients did allergic treatment seem to have any effect on the orthostatic albuminuria (Table VIII).

Essential Hematuria.—Essential hematuria in thirty-two patients who received complete urologic study was accompanied by personal allergy in five. Of these only one had major allergy; this person was skin tested and allergic management did not influence the bleeding.

Chronic Nonspecific Cystitis, Trigonitis, Urethritis.—Three hundred patients with chronic cystitis, trigonitis, and urethritis had no demonstrable infection in the urine with diagnosis confirmed by cystoscopy in all. Thirty-eight per cent, or 114 cases, had intravenous urograms, retrograde pyelograms, and kidney function tests when there was any suggestion

TABLE VIII. ALLERGIC FINDINGS IN 18 PATIENTS WITH ALLERGY AND ORTHOSTATIC ALBUMINURIA

Personal Allergy	Skin Tests	Family History Allergy	Urologic Classification
			A B C
Major-5	5	4	1 1 3
Minor-9	0	5	3 6 0
Neg.-4		4	1 3 0
18	5	13	5 10 3

TABLE IX. INCIDENCE OF ALLERGY IN 300 PATIENTS WITH CHRONIC NONSPECIFIC CYSTITIS, URETHRITIS AND TRIGONITIS

Groups	Cases	Family or Personal History Allergy	%	Personal History Allergy	%
Total	300	40	13%	35	11.7%
Chronic Trigonitis Urethritis	269	35	13%	30	11%
Interstitial Cystitis	31	5	16%	5	16%
Cystitis Trigonitis Urethritis Uncomplicated	210	34	16%	29	13%

of upper urinary tract disease. The cases were divided into two groups, group one consisting of all 300 cases without exclusion for coexisting gynecologic or urologic findings. Group two, 210 patients, had no coexisting disease. Ninety cases were excluded for the following, in order of frequency: cystocoele, stricture of urethra, chronic cervicitis and vaginitis, rectocoele, cystourethracoele, fibromyomata, and ovarian cysts. Coexisting allergy was found in 11 per cent of the entire group of 300 patients (Table IX).

Ureteral Spasm.—Of fourteen patients with ureteral spasm, two patients had a personal history of allergy, all had intravenous urograms, x-ray of abdomen, cystoscopy with calibration of ureters. The allergy in one patient consisted of skin rash from sulfonamide, and the other had chronic asthma. No allergy investigation was recorded.

Interstitial Cystitis.—The thirty-one patients with interstitial cystitis had an incidence of personal allergy in five (16 per cent). One patient was sensitive to aspirin and had positive passive transfer tests to foods. A second patient had no frank allergy, but was skin tested directly and by passive transfer technique with positive reactions to foods. In neither of these patients was any allergic regimen carried out, so the significance of these tests is not known. The other three patients were not studied with skin tests.

Enuresis.—One hundred and eighty-five cases of enuresis were reviewed. Seventeen cases (9 per cent) of the total gave a personal history of allergy, twelve with major allergies and five with minor allergies. Fifteen patients (8 per cent) were studied urologically. Six patients of those so studied (4 per cent) were found to have urologic conditions which might have explained the enuresis. When those cases who gave a family history of allergy with or without personal history of allergy are included, we find a total of twenty-six cases (14 per cent). Only one of the enuretics with a personal history of allergy was cystoscoped, and in this case stricture of the urethra was established.

SUMMARY AND CONCLUSIONS

In summary, we find that while urinary tract allergy may occur, the literature contains few reports in which both an organic basis has been completely excluded and an allergic basis incontrovertibly proved by the diagnostic studies which are described. For the skeptic, even the most convincing and suggestive cases are lacking in some important details. In our analysis of 613 patients with six urologic conditions selected because of resemblance to types reported as due to allergy and with etiology either unknown or not fully explained, we find an allergy present in 12 per cent of the group. This percentage is so similar to the accepted incidence of allergy in the general population that we do not feel justified in suspecting that allergy plays any major role in these disorders. In none of our cases who were studied completely urologically and for allergy did the allergy seem to be of etiologic significance. The consensus of clinicians in an unofficial poll is that urinary allergy is very rare.

It is interesting to speculate about this apparent immunity of the urinary tract when allergic reactions are so widespread in other systems, since the tissues of the urinary tract as elsewhere are mucous membrane, smooth muscle, and connective tissue, all of which are commonly involved in allergic reactions. The urinary tract, in contrast to the skin, respiratory

and gastrointestinal tract, has relatively little if any normal contact with foreign protein or other substances in their natural state. It is buffered by the other systems as well as by the blood and lymph, and only those substances which pass this barrier reach the urinary tract. This may be a possible explanation for the infrequency of obvious sensitivity to these agents in the urinary tract and for the difficulty with which we can demonstrate humoral or reagin type sensitivity. Allergy, which involves cellular reactions, would find the kidney no more protected than other body tissues, and we find lesions of this type as frequent or more frequent in the kidney than elsewhere. Both types of sensitivity as they affect the urinary tract are inviting fields for further study.

ACKNOWLEDGMENTS

The authors are indebted to E. P. Alyea, M.D., and John E. Dees, M.D., of the Department of Urology, Duke University School of Medicine, for the clinical cases reported in this study, and to Dr. John Dees for helpful suggestions and criticism.

REFERENCES

1. Adelsberger, Lucie, and Munter, Hans: Zur Klinik des Heufiebers. Med. Klin., 28:860-864 (June 17) 1932.
2. Adelsberger, L.: Zum Symptomenbild und zum Krankheitsverlauf der allergische Krankheiten. Deutsche med. Wchnschr., 57:585-588 (April 3) 1931.
3. Alexander, H. L., and Eyermann, C. E.: Food allergy in Henoch's purpura. Arch. Dermat. & Syph., 16:322-327 (Sept.) 1927.
4. Alyea, E. P.: Personal communication to the authors.
5. Benjamin, John A.: Personal communication to the authors.
6. Blaustein, N.: Angioneurotic edema of the entire genitourinary system. J. Urol., 16:379-390 (Nov.) 1926.
7. Bray, G. W.: Recent Advances in Allergy. Ed. 3, pp. 471-474. Philadelphia: Blakiston, 1934.
8. Brown, Alexander: Henoch-Schönlein purpura and acute nephritis due to food allergy. Glasgow M. J., 27:84-86 (March) 1946.
9. Burkland, C. E.: Dietary and occupational considerations in the treatment of urogenital disorders. Urol. & Cutan. Rev., 53:25-30 (Jan.) 1949.
10. Burkland, C. E.: Personal communication to the authors.
11. Burns, J. Edgar: Personal communication to the authors.
12. Cavelti, P. A., and Cavelti, E. S.: Studies of the pathogenesis of glomerulonephritis. III. Clinical and pathological aspects of the experimental glomerulonephritis produced in rats by means of autoantibodies to kidney. Arch. Path., 40:163-172 (Sept.) 1945.
13. Coca, A. F.: Specific sensitiveness as a cause of symptoms in disease (essential hematuria and localized retinal edema as possibly allergic symptoms). Bull. New York Acad. Med., series 2, 6:593-605 (Sept.) 1930.
14. Cook, E. N.: Misconceptions in urology. J.A.M.A., 144:1421-1423 (Dec. 23) 1950.
15. Culp, O. S.: Personal communication to the authors.
16 Danis, P. G.: Albuminuria associated with other manifestations of allergy in children. Urol. & Cutan. Rev., 45:126-128 (Feb.) 1941.
17. Dérot, M.: Evolution of acute infectious nephritis and of renal allergy. Semaine d. hôp. Paris, 24:1890-1895 (Aug. 2) 1948.
18. Dienes, L.; Ropes, M. W.; Smith, W. E.; Madoff, S., and Bauer, W.: The role of pleuropneumonia-like organisms in genito-urinary and joint disease. New England J. Med., 238:509-515 (April 8) 1948.
19. Duke, W. W.: Food allergy as a cause of bladder pain. Ann. Clin. Med., 1: 117-126 (Sept.) 1922.
20. Eisenstaedt, J. S.: Allergy of the urinary tract. J. Urol., 65:154-159 (Jan.) 1951.
21. Eisenstaedt, J. S., in discussion on Kindall, L., and Nickels, T. T.: Allergy of the pelvic urinary tract in the female. A preliminary report. J. Urol., 61:230-231 (Feb.) 1949.
22. Endicott, K. M., and Kornberg, A.: A pathological study of renal damage produced by sulfadiazine in rats. Am. J. Path., 21:1091-1099 (Nov.) 1945.

23. Fernán-Nuñez, M.: Hemoglobinuric fever; is it an allergic phenomenon? Am. J. Trop. Med., 16:563-579 (Sept.) 1936.
24. Finegold, A. N.: Anuria resulting from allergic edema following administration of sulfadiazine in a patient with asthma. J. Urol., 56:652-658 (Dec.) 1946.
25. Foley, F. E. B.: Personal communication to the authors.
26. Gairdner, D.: Schönlein-Henoch syndrome. Quart. J. Med., 17:66-95 (Apr.) 1948.
27. Goeltz, F. A.: Allergy in relation to disease of the urogenital tract. J. Urol., 37:60-63 (Jan.) 1937.
28. Gutmann, M. J.: Die allergische Erkrankungen. Med. Welt., 4:730 (May 24) 1930, 4:766 (May 31) 1930.
29. Hampton, S. F.: Henoch's purpura based on food allergy. J. Allergy, 12: 579-591 (Sept.) 1941.
30. Hand, J. R.: Interstitial cystitis; report of 223 cases. J. Urol., 61:291-310 (Feb.) 1949.
31. Harrison, J. Hartwell: Personal communication to the authors.
32. Hutton, J. E.: Favism. J.A.M.A., 109:1618-1620 (Nov. 13) 1937.
33. Jacobs, A. H.: Favism in two children in California. Pediatrics, 6:51-54 (July) 1950.
34. Jewett, Hugh J.: Personal communication to the authors.
35. Kindall, L., and Nickels, T. T.: Allergy of the pelvic urinary tract in the female. A preliminary report. J. Urol., 61:222-227 (Feb.) 1949.
36. Kittredge, W. E., and Brown, G.: Ephedrine sulfate in the treatment of nocturnal enuresis. New Orleans M. & S. J., 96:512-567 (June) 1944.
37. Kittredge, W. E., and Johnson, C.: Allergic hematuria due to milk. New Orleans M. & S. J., 101:419-421 (Mar.) 1949.
38. Kornberg, A.; Endicott, K. M.; Daft, F. S., and Sebrell, W. H.: The influence of casein and other agents on the production of renal lesions by sulfadiazine and acetyl-sulfadiazine. Pub. Health Rep., 60:661-675 (June 15) 1945.
39. Kruse, H., and McMaster, P. D.: The distribution and storage of blue antigenic azoproteins in the tissues of mice. J. Exper. Med., 90:425-446 (Nov.) 1949.
40. Lazarus, J. A.: Idiopathic (Schönlein's) purpura associated with hematuria. J. Urol., 62:354-360 (Sept.) 1949.
41. Leeks, H. I.: Favism, report of a case in a child. J. Pediat., 34:309-314 (Mar.) 1949.
42. Lich, Robert, Jr.: Personal communication to the authors.
43. McCrae, T., and Ullery, J. C.: Favism. J.A.M.A., 101:1389-1391 (Oct. 28) 1933.
44. Mainwaring, W. H., and Marino, H. D.: Reactions of the urinary bladder in rabbit anaphylaxis. J. Immunol., 13:69-72 (Jan.) 1927.
45. Marchetti, Andrew A.: Personal communication to the authors.
46. Marshall, Victor F. (New York): Personal communication to the authors.
47. Miller, M. W., and Uhle, C. A.: A survey of urinary tract allergy. Internat. Clin., 3: new series 2:183-191 (Sept.) 1939.
48. Nickels, T. T.: Personal communication to the authors.
49. Nugent, James J.: Personal communication to the authors.
50. Osler, W.: Practice of Medicine. P. 317. New York: D. Appleton and Co., 1893.
51. Peters, J. H.: Reiter's syndrome with keratotic dermatitis. Arch. Dermat. & Syph., 59:217-229 (Feb.) 1949.
52. Pressman, D.: The zone of localization of antibodies. IV. The in vivo disposition of anti-mouse-kidney serum and anti-mouse plasma serum as determined by radioactive tracers. J. Immunol., 63:375-388 (May) 1949.
53. Quinby, W. C., quoted by Harrison, J. H.: Personal communication to the authors.
54. Rackemann, F. M.: Allergy. Arch. Int. Med., 81:696-745 (May) 1948.
55. Rattner, H.: Dermatitis of the penis from rubber. J.A.M.A., 105:1189 (Oct. 12) 1935.
56. Rhodes, John: Hematuria after the use of tetanus antitoxin. Report of a case. J. Urol., 38:410-411 (Oct.) 1937.
57. Rhodes, John: Personal communication to the authors.
58. Ross, J. F.: Hemoglobinemia and the hemoglobinurias. New England J. Med., 233:691-696 (Dec. 6) 1945; 732-737 (Dec. 13) 1945; 766-771 (Dec. 20) 1945.
59. Rudolf, G. deM.: The ephedrine treatment of nocturnal enuresis. J. Ment. Sc., 94:629-640 (July) 1948.
60. Rytand, D. A.: Fatal anuria, the nephrotic syndrome and glomerular nephritis as sequels of the dermatitis of poison oak. Am. J. Med., 5:548-560, (Oct.) 1948.
61. Rytand, D. A.; Burnham, D. W., and Cox, A. J., Jr.: Periarteritis nodosa fol-

lowing the dermatitis of poison oak and of primrose. Stanford M. Bull., 6:319-323 (May) 1948.
62. Salen, E. B.: Ist die Sensibilisierung bei der Allergie Ubiquitär? Allergische Reaktion der Harnweges. Acta med. Scandinav., 78:197-203 (May) 1932.
63. Sargent, J. C.: Reiter's syndrome. J. Urol., 54:556-564 (Dec.) 1945.
64. Solomon, A. A.: Effect of arsenotherapy in upper urinary tract changes in infectious abacterial pyuria. J. Urol., 59:252-257 (Feb.) 1948.
65. Solomon, D. H.; Gardella, J. W.; Fanger, H.; Dethier, F. M., and Ferrebee, J. W.: Nephrotoxic nephritis in rats. J. Exper. Med., 90:267-272 (Sept.) 1949.
66. Stefanini, M.; Roy, C. A.; Zannos, L., and Dameshek, W.: Therapeutic effect of pituitary adrenocorticotropic hormone (ACTH) in a case of Henoch-Schönlein vascular (anaphylactoid) purpura. J.A.M.A., 144:1372-1374 (Dec. 16) 1950.
67. Taylor, A. W., and Jacoby, N. M.: Acute polyarteritis nodosa in childhood. Lancet, 257:792-794 (Oct. 29) 1949.
68. Thomas, J. W., and Wickstein, V. P.: Allergy in relation to the genito-urinary tract. Ann. Allergy, 2:396-403 (Sept.-Oct.) 1944.
69. Tzank, A., and Cottet, J.: Les intolerances renales. Presse med., 42:415-419 (Mar. 14) 1934.
70. Vaughan, W. T., and Hawke, E. K.: Angioneurotic edema with some unusual manifestations. J. Allergy, 2:125-129 (Jan.) 1931.
71. Vest. S. A.: Personal communication to the authors.
72. Vogl, A.: Colica Mucosa der Harnblase. Wien klin. Wchnschr., 48:756 (May 24) 1935.
73. Wagley, P. F.; Zinkham, W. H., and Siebens, A. A.: A note on studies of hemolysis in paroxysmal (cold) hemoglobinuria. Am. J. Med., 2:342-346 (Apr.) 1947.
74. Weyrauch, H. M.: Personal communication to the authors.
75. Young, H. H., (Baltimore); Haines, J. S., and Prince, C. L.: Orthostatic albuminuria; importance of its recognition by medical examining boards. Mil. Surgeon, 92:353-365 (April) 1943.

PULMONARY DISTRIBUTION OF RADIOACTIVE PARTICLES IN RABBITS AFTER INHALATION AND INTRAVENOUS INJECTION

(Continued from Page 713)

23. Prigal, S. J.; Brooks, A. M., and Harris, R.: The treatment of asthma by inhalation of aerosol aminophylline. J. Allergy, 18:16, 1947.
24. Segal, M. S., and Ryder, C. M.: Penicillin inhalation therapy. New England J. Med., 236: 132, 1947.
25. Taplin, G. V.; Grevior, J. S., and Drusch, H.: Pulmonary penetration of fine particles administered by intratracheal insufflation and inhalation. Ann. Western Med. & Surg., 4:391, 1950.
26. Taplin, G. V., and Bryan, F. A.: Administration of micronized therapeutic agents by inhalation or topical application. Science, 195:520, 1947.
27. Taplin, G. V., and Bryan, F. A.: The use of micronized therapeutic agents by inhalation with special reference to allergic pulmonary conditions. Ann. Allergy, 6:42, 1948.
28. Taplin, G. V.; Greene, W.; Ralston, W.; Adolph, W., and Baurmash, L.: Micropowdered procaine penicillin by inhalation. Ann. Allergy, 8:396, 1950.
29. Tremble, G. E.: Clinical observations on the movement of nasal cilia, an experimental study. Laryngoscope, 58:206, 1948.
30. Van Wijk, A. M., and Patterson, H. S.: Percentage of particles of different sizes removed from dust laden air by breathing. J. Indust. Hyg. & Toxicol., 22:31, 1940.
31. Weinberg, S. J., and Parker, G. L.: Aerosol and micronized ephedrine and penicillin therapy of diseases of the lower respiratory tract. Arch. Int. Med., 84: 389, 1949.

Atomic Energy Project, University of California,
Postoffice Box 4164, West Los Angeles 24

PHENERGAN: A CLINICAL EVALUATION

Based on a Study of 193 Allergic Patients

M. MURRAY PESHKIN, M.D., F.A.C.A.
HOWARD G. RAPAPORT, M.D., F.A.C.A.
and
SAMUEL GROSBERG, MD., F.A.C.A.
New York, New York

MANY synthetic antihistaminic drugs are employed in this country. However, this study on a representative series of patients was prompted by the desirability and practicality of employing a chemical compound with the reported combined highest antihistaminic and prolonged therapeutic action. This drug, relatively new to this country, is called Phenergan and was initially referred to as RP 3277 (N-[2'-dimethylamine-2' methyl] ethyl phenothiazine), which for medical purposes is prepared as the hydrochloride. Phenergan was introduced in 1946 by Halpern[5,9] of France, who has claimed it to be the most powerful of the antihistaminic drugs.

Halpern and his associates[16,17] usually employed Phenergan in doses of from 50 to 100 mg a day, but smaller amounts were at times effective. Some patients, however, required 150 mg or more for control of their allergic disorders. It was reported that urticaria responded well in all but one of forty-seven cases and in all of eight cases of angioedema. The treatment failed in the majority of the cases of eczema, but itching was often relieved. Of thirty-eight cases of hay fever, thirty-six were considerably or completely relieved after the first dose. No other product has given as good results in their experience. Eleven of twenty-one cases of asthma showed appreciable to complete disappearance of symptoms. Migraine was favorably influenced in four of ten cases. These results are largely confirmed by the published reports on Phenergan by other workers on the Continent.[1,2,12,19] In this country, Waldbott[18] reported its use in twenty-nine cases of hay fever and allergic rhinitis, with marked relief in 62 per cent; in fifteen cases of urticaria and angioedema, with marked relief in 75 per cent; and marked relief in 25 per cent of twenty cases of bronchial asthma. In most instances only three to five doses each of 50 mg of the drug were given. It was found to possess a decidedly more protracted action than other antihistaminic drugs and therefore was recommended for use to greatest advantage before bedtime. Shulman[14] reported fifty-five allergic patients who failed to respond to the commonly used antihistaminic drugs. Phenergan was then given orally in a single daily dose ranging between 6.5 to 25 mg immediately after the evening meal. The average number of days per patient the drug was ingested was not stated but due to a limited supply the time of usage was relatively short. Of the fifty-five patients with various

The Phenergan used in this study was supplied by Wyeth, Incorporated, Philadelphia, Pennsylvania.

Approved for publication September 6, 1951.

allergic disorders (excluding hay fever), thirty-one patients (51 per cent) showed marked improvement to complete relief of symptoms. Patients with urticaria showed the highest incidence (100 per cent) of excellent results.

The purpose of this study is to determine (1) the comparable clinical response to Phenergan in children and adults with various allergic syndromes, (2) the effect of longer periods of ingestion of the drug than those already reported in the literature, (3) toxicity of the drug given in comparable doses to children and adults, and (4) its effectiveness as a single daily dose.

MATERIALS AND METHODS

One hundred and ninety-three patients (71 children and 122 adults) were studied. The ages of the children ranged from two to fifteen years and of the adults from seventeen to sixty-seven years, averaging 9.5 and thirty-eight years per group of patients, respectively. The total number of allergy syndromes treated was 351.

In the large majority of patients dietetic and/or specific allergy immunization treatments were administered previous to and also during the period when Phenergan was employed. In other words, it was largely employed as an adjunctive therapeutic measure on a selected group of allergic patients with the view to further enhance the positive results from specific allergenic treatment or to obtain some relief for those patients who failed to respond to their respective allergy treatments. It should be emphasized that patients who responded satisfactorily to allergy treatments alone were not included in this study. In other words, we wished for the most part to determine its value in patients who received only partial or no benefit from specific allergy immunization or dietetic treatment or avoidance measures or from the employment of any combination of these three methods of treatment. For example, if a patient with hay fever failed to respond to specific pollen therapy, particularly during the height of the pollen season, and the addition of Phenergan afforded moderate relief from symptoms, then the value of the drug is appreciated. On the other hand, if for another patient with only a moderate response to pollen therapy it could afford satisfactory relief from symptoms, then the usefulness of such a drug in this case is easy to evaluate. However, the use of any antihistamine to the exclusion of specific immunization treatment especially in the instance of nasal allergy, seasonal or perennial, is to be discouraged, because a broad experience in these patients strongly points to an increased tendency for the development of asthma. We were not interested in prescribing the drug, for example, to every patient receiving specific pollen immunization in order to insure maximum therapeutic response. Such studies have been reported in the literature, and this practice is commonly employed. It is to be expected that the therapeutic response in such a group of patients would be more efficacious than for a comparable group of patients receiving pollen immunization alone. In this study the therapeutic worth of Phenergan was investigated according to clinical research procedures.

TABLE I. NUMBER OF DAYS PHENERGAN WAS ADMINISTERED TO 193 PATIENTS WITH VARIOUS ALLERGIC CONDITIONS

Major Syndrome*	Number of Patients	Number of Days of Treatment						Average Number of Days Per Patient
		7 14	15 30	31 60	61 100	101 200	201 300	
Pollen Allergy	108	18	29	35	11	14	1	52
Perennial Rhinitis	51	14	4	13	3	15	2	78
Perennial Asthma	21	1	3	4	4	9	0	94
Eczema Neurodermite†	7	2	0	2	2	1	0	55
Angioedema and Urticaria	6	2	0	0	1	2	1	99
Total	193	37	36	54	21	41	4	64

*Major allergy syndrome refers to that condition which disturbed the patient most and for which treatment was primarily sought. In the case of pollen allergy, hay fever with or without pollen asthma, there may also be clinical evidence of perennial allergic rhinitis, urticaria, perennial asthma and neurodermite, all of which were regarded as secondary to the major disturbing pollen allergy.
†Includes one case of vernal conjunctivitis, for convenience of recording.

The patients in this study, with a number of exceptions, ingested 25 mg of Phenergan in a single dose up to two doses before bedtime, without comment except with directions for its use. Questions with respect to the clinical response and side effects from the drug were asked indirectly. Only those patients were included in this study who took Phenergan for at least one week.

CLINICAL EVALUATION

The difficulties in a clinical evaluation of this type of study are readily apparent. Nevertheless, the voluntary statements of the patient's parents or the patient's own evaluation of Phenergan, together with the notes recorded in detail from our own observations, afforded ample data from which definitive conclusions could be drawn. Therapeutic response was classified as satisfactory, moderate, or none. Patients with a negative response included all those failing to obtain at least 50 per cent relief from their current allergy symptoms. Patients obtaining 50 to 75 per cent relief and those with 75 to 100 per cent relief are recorded as having a moderate and satisfactory response, respectively.

Table I shows the 193 allergic patients grouped according to the major allergy condition for which they consulted us. It may be noted that the number of days of therapy ranged from seven to 300, the average number of days per patient being sixty-four. The total number of doses administered was about 13,000. The dosage will be discussed under a separate heading.

Table II reveals the therapeutic response in 193 patients with respect to the total number of allergy syndromes (351). In this table each allergy syndrome is counted as a separate case. A patient with hay fever due to trees, grass, and weeds is recorded as having three separate allergy syndromes.

It should be noted (Table II) that when hay fever occurred alone, the satisfactory therapeutic response was significantly higher (51 per cent) than the response for the cases with hay fever associated with other al-

TABLE II. THERAPEUTIC RESPONSE TO PHENERGAN IN 193 ALLERGIC CHILDREN AND ADULTS WITH 351 ALLERGY SYNDROMES, COUNTING EACH ALLERGY SYNDROME AS A CASE

Allergy Syndrome	Number of Cases	Therapeutic Response					
		Satisfactory		Moderate		None	
		Number	Per Cent	Number	Per Cent	Number	Per Cent
Hay Fever							
Alone	82	42	51	19	23	21	26
Mixed*	81	17	21	33	41	31	38
Total	163	59	36	52	32	52	32
Perennial Rhinitis							
Alone	33	13	39	12	36	8	25
Mixed*	69	18	26	23	33	28	41
Total	102	31	30	35	34	36	36
Asthma							
Pollen	21	1	5	0	0	20	95
Perennial	34	1	3	0	0	33	97
Total	55	2	4	0	0	53	96
Eczema or Neurodermite	13	2	15	1	8	10	77
Conjunctivitis							
Vernal	3	0	0	2	67	1	33
Perennial	3	0	0	2	67	1	33
Total	6	0	0	4	67	2	33
Migraine and Allergic Headache	2	0	0	1	50	1	50
Angioedema and Urticaria	6	3	50	2	33	1	17
Urticaria	4	3	75	1	25	0	0
Grand Total	351	100	29	96	27	155	44

*Mixed refers to the other allergy syndromes affecting the patient.

lergies (21 per cent). It is not surprising, then, to note that the incidence of moderate response for the group of patients with hay fever alone as compared to the group of patients with mixed hay fever was 23 and 41 per cent, respectively. Thus, when the total incidence of moderate and satisfactory therapeutic response for hay fever alone and hay fever mixed is noted as being 74 and 62 per cent respectively, a difference not statistically significant, the true picture of its effectiveness in hay fever is not revealed.

The total comparative incidence of moderate and satisfactory therapeutic response for patients with perennial allergic rhinitis alone and mixed was 75 and 59 per cent, respectively. These figures are not surprising in view of the frequent complications present in the mixed perennial rhinitis.

The total incidence of moderate and satisfactory clinical response to Phenergan in the patients with urticaria and angioedema and urticaria alone was 83 and 100 per cent, respectively, the highest incidence recorded for all of the allergy syndromes treated.

The total comparative incidence of moderate and satisfactory response in the cases with asthma, eczema (neurodermite), migraine and allergic headache, and allergic conjunctivitis, was 4, 23, 50 and 67 per cent, respectively.

A breakdown of the eighty-one cases of mixed hay fever is of interest. Response for hay fever with secondary perennial allergic rhinitis was satisfactory for hay fever in 32 per cent, moderate in 41 per cent, and none in 27 per cent. The response for hay fever with pollen asthma was satisfac-

TABLE III. THERAPEUTIC RESPONSE TO PHENERGAN IN 71 ALLERGIC CHILDREN WITH 142 ALLERGY SYNDROMES, COUNTING EACH ALLERGY SYNDROME AS A CASE

Allergy Syndrome	Number of Cases	Therapeutic Response					
		Satisfactory		Moderate		None	
		Number	Per Cent	Number	Per Cent	Number	Per Cent
Hay Fever							
Alone	20	14	70	3	15	3	15
Mixed	42	8	19	11	26	23	55
Total	62	22	35	14	23	26	42
Perennial Rhinitis							
Alone	15	8	53	3	20	4	27
Mixed	31	8	26	6	19	17	55
Total	46	16	35	9	19	21	46
Asthma							
Pollen	11	1	9	0	0	10	91
Perennial	13	1	8	0	0	12	92
Total	24	2	8	0	0	22	92
Eczema or Neurodermite	7	1	14	0	0	6	86
Conjunctivitis							
Vernal	1	0	0	1	100	0	0
Perennial	2	0	0	1	50	1	50
Total	3	0	0	2	67	1	33
Grand Total	142	41	29	25	18	76	53

tory for hay fever in 16 per cent, moderate in 48 per cent, and none in 36 per cent. The response for hay fever secondary to perennial allergic rhinitis was satisfactory in 0 per cent, moderate in 8 per cent, and none in 92 per cent. The response for hay fever secondary to perennial asthma was satisfactory in 20 per cent, moderate in 20 per cent, and none in 60 per cent. In other words, the total incidence of favorable therapeutic response for cases with hay fever associated with another allergy syndrome is high (average 69 per cent) when hay fever is the primary and major allergy, but when hay fever is secondary to other allergies the incidence of favorable therapeutic response for hay fever is low (average 22 per cent).

When the cases of hay fever with and without secondary perennial allergic rhinitis were evaluated, it was noted that the incidence of positive therapeutic response was lower for ragweed than for grass sensitization, 59 and 78 per cent, respectively. This observation is as expected from the point of view of response to specific pollen immunization, potency and toxicity of pollen, and the differences in the climatic variations occurring with the grass (summer) and ragweed (fall) seasons. These observations are of further importance considering the incidence of therapeutic response for Phenergan in hay fever reported in Europe and other areas where ragweed pollen season is nonexistent. The number of tree cases were too few to be statistically significant.

When the statistics in Table II are separated for children (Table III) and for adults (Table IV), the differences of the comparative incidences of therapeutic response to Phenergan are noteworthy. Children with hay fever alone showed a satisfactory response of 70 per cent, while a comparable response of only 45 per cent occurred in adults. Failure in children and

TABLE IV. THERAPEUTIC RESPONSE TO PHENERGAN IN 122 ALLERGIC ADULTS WITH 209 ALLERGY SYNDROMES COUNTING EACH ALLERGY SYNDROME AS A CASE

Allergy Syndrome	Number of Cases	Therapeutic Response					
		Satisfactory		Moderate		None	
		Number	Per Cent	Number	Per Cent	Number	Per Cent
Hay Fever							
Alone	62	28	45	16	26	18	29
Mixed	39	9	23	22	56	8	21
Total	101	37	37	38	38	26	25
Perennial Rhinitis							
Alone	18	5	28	9	50	4	22
Mixed	38	10	26	17	45	11	29
Total	56	15	27	26	46	15	27
Asthma							
Pollen	10	0	0	0	0	10	100
Perennial	21	0	0	0	0	21	100
Total	31	0	0	0	0	31	100
Neurodermite	6	1	17	1	17	4	66
Conjunctivitis							
Vernal	2	0	0	1	50	1	50
Perennial	1	0	0	1	100	0	0
Total	3	0	0	2	67	1	33
Migraine and Allergic Headache	2	0	0	1	50	1	50
Angioedema and Urticaria	6	3	50	2	33	1	17
Urticaria	4	3	75	1	25	0	0
Grand Total	209	59	28	71	34	79	38

adults was 15 and 29 per cent, respectively, whereas in the instances of mixed hay fever, the incidence was 55 and 38 per cent, respectively. In children with perennial allergic rhinitis, the drug produced a satisfactory response in 53 per cent as compared with 39 per cent for adults. Failure for children and adults was about equal, 25 per cent, whereas for the mixed cases the incidence of failure was 55 and 41 per cent, respectively. In children with perennial and pollen asthma, a satisfactory result occurred in only 8 per cent as compared with 0 per cent in adults. Failure for children and adults was 92 and 100 per cent, respectively. Satisfactory relief from eczema and neurodermatitis for children and adults was negligible.

The need for treatment with Phenergan for patients with acute or chronic angioedema and urticaria or for urticaria alone, was confined to adults. The incidence of positive therapeutic response (satisfactory and moderate) for these conditions was 83 and 100 per cent, respectively. Thus, a higher incidence of relief for cases with angioedema or urticaria than for any other allergy syndrome was observed. The only failure occurred in a woman, aged forty-five years, with chronic angioedema and urticaria of eight years' duration. For ninety days she ingested 100 mg each day in three divided doses. The initial onset of the dermatoses was sudden and dramatic. She was gripped with extreme anxiety about her only son who was inducted into the Army of the U. S. during World War II. During one winter she entrained for a southern vacation resort. On arrival and while walking on the station platform, she spotted a group of soldiers marching nearby. Within a matter of minutes angioedema and urticaria

ensued and rapidly became generalized. These lesions have varied in size and distribution but have always remained despite her recognition of the precipitating cause. She rejected (after careful preparation) the recommendation for deep psychotherapy.

PENICILLIN HYPERSENSITIVITY

Phenergan gave dramatic relief from severe generalized angioedema and urticaria caused by penicillin when the commonly employed antihistaminic drugs failed. In the case of a physician who had ingested 200 mg of Benadryl daily, in four divided doses, and then changed to Pyribenzamine in similar dosage for a total period of one week, the uncontrolled angioedema and urticaria were aggravated by the unpleasant side effects of these drugs, namely, extreme restlessness, excitability, insomnia, and fright. Phenergan, 25 mg, was orally administered twice daily for three days and once daily for another four days. A rapid soporific reaction followed the first dose, and after the second dose the dermatoses were markedly relieved. The rash was entirely cleared by the fourth day. He slept well every night.

Similar if not more dramatic response to Phenergan for relief of dermatoses following penicillin injections is related in the following case report.

Patient, *j.* M., textile executive, a white, married man, aged fifty years, on November 13, 1950, consulted Dr. S. Meylackson, New York, N. Y. The history revealed that penicillin had been frequently injected during the preceding two years for recurrent respiratory and "sinus" infections, with tolerance. On October 25, 1950, a complete physical examination revealed no abnormalities. On October 30 and November 6, penicillin was injected for the control of "sinus congestion." On November 9, the local site of the last injection of penicillin became hot, swollen, and itchy. On November 12, a generalized angioedema and urticaria appeared. The cutaneous pruritus was intense. The following day a dermatologist injected epinephrine hydrochloride, and Neo-Antergan in maximum dosage was ingested. Skin lotions and medicated baths were also prescribed. November 13, the dermatoses worsened. The patient was markedly apprehensive and agitated. He pleaded for relief from the insufferable pruritus and for some sleep. On November 14, the temperature was elevated up to 102.3° F. The dermatoses had become more confluent, especially about the trunk and thighs. In certain areas the lesions assumed an elevated, circinate appearance. The rash on the neck, fingers, and feet had become markedly violaceous, assuming a purpuric character. Despite the treatment the patient had not slept and could not refrain from continual scratching. The white blood cell count was 13,400. The differential count was normal. Other physical and laboratory findings were normal except for a pulse rate of 100.

On the morning and evening of November 15, with the skin lesions as described and the angioedema and urticaria at its worst, Phenergan, 25 mg, was intramuscularly injected. One-half hour after the morning injection the pruritus was markedly lessened. The patient relaxed and slept for short periods. After the evening injection, he slept through the night. The following morning he awoke moderately drowsy but refreshed to find the angioedema and urticaria markedly relieved. For the following three days 25 mg of Phenergan was ingested twice daily. For the remaining three days only a single daily dose of 25 mg was given. On November 17, the temperature and complete blood count were normal. The rash rapidly subsided and by the seventh day was cleared except for slight residual faded purpuric spots on the fingers.

TABLE V.

SIDE-REACTIONS IN 193 ALLERGIC PATIENTS TREATED WITH PHENERGAN

Major Allergy Syndrome	No. of Cases	Age in Years	Side Reactions											
			Drowsiness											
			Alone	Dizzy	Fatigue	Dizzy Vomiting	Depression	Dryness Throat	Fatigue	Headache	Abd. Colic	Insomnia	Total	Per Cent
CHILDREN														
Pollen Allergy	38	4–15	10	1	1	1	0	0	1	1	0	1	16	42
Perennial Rhinitis	22	3–15	4	0	1	0	0	0	0	0	0	0	5	23
Perennial Asthma	7	2–14	2	0	1	0	0	0	0	0	0	0	3	43
Eczema Neurodermite	3	2–10	0	0	0	0	0	0	1	0	0	0	1	33
Vernal Conjunctivitis	1	8	0	0	0	0	0	0	0	0	0	0	0	0
Total	71	2–15	16	1	3	1	0	0	2	1	0	1	25	35
ADULTS														
Pollen Allergy	70	17–61	28	2	1	0	2	2	4	1	0	0	40	57
Perennial Rhinitis	29	17–62	8	0	0	1	1	0	0	0	1	1	12	41
Perennial Asthma	14	20–67	8	0	0	0	0	0	0	0	0	0	8	57
Eczema Neurodermite	3	22–58	0	0	1	0	0	0	0	0	0	0	1	33
Angioedema & Urticaria	6	32–58	6	0	0	0	0	0	0	0	0	0	6	100
Total	122	17–67	50	2	2	1	3	2	4	1	1	1	67	55
Grand Total	193	2–67	66	3	5	2	3	3	5	2	1	2	92	48

SIDE REACTIONS

The type and incidence of side reactions from Phenergan is shown in Table V. A grand total of ninety-two side reactions occurring in 193 allergic patients, an incidence of 48 per cent, assume greater significance when the reactions are studied separately for children and adults.

Side Reactions in Children.—Twenty-five children (35 per cent) had side reactions. Drowsiness with dizziness, fatigue, or vomiting occurred in five children (7 per cent) and drowsiness alone in sixteen children (22 per cent). Thus, drowsiness, the most common reaction, occurred in twenty-one children (29 per cent). Of the remaining reactions, fatigue alone occurred in two children, headache alone in one child, and insomnia alone in one child, or 3, 1.5, and 1.5 per cent, respectively.

An analysis of the side reactions in relation to dosage is as follows: four of these twenty-five children were given a single daily dose of 12.5 mg of Phenergan. The remaining twenty-one children were given 25 mg before bedtime. In three of these children an additional 12.5 mg of the drug was given either at bedtime or during the early afternoon. In another four children with pollen allergy the single daily dose was subsequently reduced from 25 to 12.5 mg.

While a single daily dose of 12.5 mg as compared to 25 mg may reduce the degree and incidence of side reactions in children, the therapeutic re-

sponse may also be reduced. The ideal and most effective initial dose for children is a single daily dose of 25 mg ingested one hour before bedtime. This dose can be adjusted up or down depending upon the child and the allergy syndrome treated. With continual use, side effects in many instances clear after one to thirty days of use. In only one child was it found desirable to discontinue its use because of troublesome insomnia.

Children with multiple seasonal hay fever respond better during the grass than during the ragweed pollen season. During the height (middle third) of the pollen seasons, especially the fall season, the therapeutic response to a stationary dose of the drug frequently is poor or moderate as compared to a satisfactory response recorded for the first and third periods.

There appears to be no correlation between the therapeutic response from a daily dose of 25 or 50 mg and side ractions. In the dosage used it is a safe, dependable, and desirable antihistaminic drug for allergic children.

In the group of forty-six children without side reactions from Phenergan, the experience with dosage and therapeutic response was comparable to that obtained for the group of twenty-five children with side reactions. In a few cases of the former group it was noted that when the dose was stepped up from 25 to 37.5 mg, drowsines or abdominal colic occurred.

Side Reactions in Adults: Sixty-seven side reactions occurred in 122 adults (55 per cent). Drowsiness with dizziness, fatigue, vomiting, or depression occurred in eight adults (7 per cent) and drowsiness alone in fifty adults (41 per cent). Thus, drowsiness occurred in fifty-eight adults (48 per cent). Of the remaining side reactions occurring alone, dryness of the throat affected two adults, fatigue four adults, and headache or abdominal colic or insomnia one adult each, with a respective incidence of 1.5, 3, 0.8, and 0.8 per cent.

An analysis of the side reactions with respect to dosage is as follows: all of the sixty-seven patients ingested not less than one daily dose of 25 mg before bedtime. Four patients with pollen allergy discontinued the drug after eight to twenty-nine days because of excessive drowsiness extending through the daytime for three of them, and in the remaining patient during eleven days of inability to gauge the distance between her feet and stairs and curbstones, when stumbling became disturbing and dangerous. In two of these four patients the therapeutic response was satisfactory, and in the other two patients it was poor.

In eight patients the single dose was subsequently reduced from 25 to 12.5 mg. In another group of twelve patients the daily dose was stepped up from 25 to as high as 100 mg.

Fifty-five patients showed no side reactions. Thirty of these patients had a total of thirty-eight pollen syndromes (counting each pollen season as a separate syndrome) and were given daily doses of 25 mg or more with an incidence of poor therapeutic response for grass and ragweed hay fever of 22 and 37 per cent, respectively.

The clinical observations with respect to side reactions in children in the main apply to adults, with the exception that tolerance of children is better than of adults. This is evident from the significantly lower incidence (35 per cent) of side reactions for children as compared to 55 per cent for adults. The side reactions are less prolonged and less severe in children than in adults, and the removal of the drug quickly clears the side reactions. The common side effect of drowsiness in older children and adults is readily controlled with a morning dose of 2.5 to 5 mg of Benzedrine or Dexedrine sulfate. However, Phenergan had to be discontinued in one child (1.4 per cent) and in four adults (3.3 per cent) because of disturbing side reactions.

PHENERGAN AND PREGNANCY

One patient, aged twenty-three years, with slight drowsiness and satisfactory therapeutic response to a daily dose of 25 mg, subsequently became pregnant. During this period she had symptoms of perennial allergic rhinitis and was obliged to increase the daily dose to 50 mg to maintain a satisfactory response over a period of forty-six days, without ill effect to herself or to the offspring.

Another woman, aged thirty-two years, with perennial allergic rhinitis took 25 mg daily for 300 days. This period included the first seven months of pregnancy. There were no side reactions, but the therapeutic response was poor. Neither the patient nor the offspring had ill effects from the drug, which was taken to control insomnia.

PHENERGAN AND SLEEP

Our figures concerning the effect on sleep were based only on the statement of the patient. Twenty-six patients with side reactions and an equal number without side reactions were studied. Twenty-five patients (96 per cent) with side reactions reported to have slept more soundly or restfully and longer than usual, while one patient (4 per cent) slept poorly. Sixteen patients (62 per cent) without side reactions slept well, and ten patients (38 per cent) slept poorly. The soporific action of 25 mg per day lasts for many months and in this respect surpasses any other antihistaminic drug. Some patients appear to develop a tolerance for the drug and so are obliged to increase the dose to 50 mg to maintain its soporific action. In the latter instance, the increased dose at times induces morning drowsiness. The remarks of patients on the effect of Phenergan on sleep are of interest: "Slept wonderfully," "slept like I was knocked out for the first week," "slept like a log," "slept like in a trance," and "best sedative."

It has now become our common practice to employ Phenergan as a substitute soporific, especially for patients with sensitiveness to barbiturates and other soporific drugs or in patients with dermatoses in whom dermatrophic drugs should be avoided. Miller and Hurst[12] employed Phenergan in a series of thirty patients with tuberculosis and found the

drug to be an excellent soporific. We have not yet observed one patient to evidence allergic symptoms from prolonged use of Phenergan.

PHENERGAN AND BLOOD AND URINE

Ten patients ingested 25 mg or more as a single daily dose for an average of 104 days per patient. White and red blood cells and differential counts and urinalysis were done several or more times on each patient. All the findings were normal.

In the doses employed in this study of 71 children and 122 adults in whom Phenergan was given for an average of sixty-four days per patient, the usual daily dose being 25 mg (the range between 12.5 and 75 mg), clinical evidence of convulsion, "sore throat," granulocytopenia, or other serious toxic manifestation was not observed. This statement can now be applied to an experience with an additional 100 patients.

PHENERGAN AND CUTANEOUS SENSITIZATION TESTS

In the dosage employed, Phenergan did not inhibit or even diminish the size of the cutaneous diagnostic sensitization tests as commonly employed in allergy practice.

PHENERGAN, PLAIN AND ENTERIC COATED

In eleven patients, Phenergan was given as an enteric coated tablet as a substitute for the uncoated or plain tablet for purposes of determining whether side reactions could be lessened or eliminated and also if the therapeutic response to the drug could be enhanced. The therapeutic response seemed to be about the same for either preparation. The enteric coated tablet was ingested after the evening meal and the uncoated drug taken at bedtime. Our findings suggest that side reactions with uncoated tablets may be lessened or eliminated when replaced by the enteric coated preparation. The possibility of obtaining a lower incidence of favorable therapeutic response with the enteric coated as compared with the plain drug must be entertained.

THE PROTRACTED ACTION OF PHENERGAN

One of the prime reasons for engaging in a careful clinical study of Phenergan was its reputation as a long-acting antihistaminic drug of high potency and pharmacologic action. The experience obtained in this and a new series of cases clearly indicates that compared dose for dose with the other available antihistaminic drugs Phenergan is not only the longest acting but in some respects the most efficacious preparation. However, the soporific action of Phenergan surpasses that of all other antihistaminic drugs. If the patient is ambulant, then it becomes mandatory that Phenergan be administered only before bedtime. The soporific action for many reasons makes it an especially desirable antihistaminic drug. When there are no side reactions and when relief from allergy symptoms lasts for only

twelve hours or less, as has been observed in some cases, an additional daytime dose of 12.5 to 25 mg can be administered safely. When side reactions occur and it is found necessary to administer a daytime dose, any of the milder antihistaminic drugs can be given. This was done in seventeen cases in this study. In four of these patients the therapeutic response with the supplemental drugs continued to be poor, while in the remaining thirteen cases the response was maintained as moderate or satisfactory. It should be emphasized that the milder antihistaminic drugs administered alone to these patients failed to obtain comparable levels of relief as when Phenergan was employed as the basic antihistaminic drug. The supplemental use of the milder antihistaminic drugs is most frequently needed during the middle third or the height of the pollen seasons, particularly the weed season.

DISCUSSION

This study was not concerned with the role of histamine in allergic disorders nor with any theories concerning the histamine basis for allergy. Our primary interest was to determine the therapeutic response to and tolerance for Phenergan in patients of all ages with allergic disorders. Moreover, we largely employed Phenergan as an adjunctive measure of treatment.

The term "antihistamine" as applied to Phenergan and related drugs is an unfortunate selection because it, in many respects, is misleading and confusing. When all the pharmacological and clinical evidence is carefully sifted, we become more impressed with Halpern's[7] desire to delete this term from any discussion of these drugs. Halpern[7] does not support the currently accepted histamine theory of allergy. The term "antihistamine," however, seems to be with us to stay, and for the moment the term will be employed but with reservation as to its meaning. A brief review of some of Halpern's important pharmacologic researches on Phenergan will be of interest. Halpern[10] reported the remarkable effect of Phenergan on capillary resistance in allergy affections, and its preventive action in fatal acute edema of the lungs in the rabbit. Of note is the disparity between the extraordinary general antihistaminic power of Phenergan and its almost total ineffectiveness on the excretory power of histamine on gastric secretion, as shown by the fact that animals which have been protected against 300 to 400 lethal doses of histamine have developed gastric ulcers, some of which perforated the peritoneum within twenty-four hours to several days, resulting in fatal peritonitis.[11] Phenergan has been shown to be as much as seven times more potent than the antihistamine with which it was compared, with approximately three times the duration of action.

Phenergan inhibits the Arthus phenomenon,[3] an effect not reported with other antihistaminic drugs.

Halpern[15] induced in normal guinea pigs severe asthmatic states by administration of histamine by aerosol. The animals with anaphylactic asthma had bronchial edema, and the animals with pharmacodynamic asthma did

not. Rapid and complete relief resulted from an antihistamine injection given to the animals in the course of an attack of histamine asthma due to bronchospasm, i.e., to a reversible and functional disturbance. The antihistamine injection proved ineffective when given in the course of an attack of anaphylactic asthma due to bronchial edema, in the presence of which the antihistaminic drug can no longer exert its effect on the capillary permeability. However, when the antihistaminic drug was given before the attack of either anaphylactic or antihistaminic asthma, the injection prevented the attack of either type of asthma.

These observations along with only the prophylactic protection of Phenergan against the epinephrine, chloropicrin, and phosgene gas-induced pulmonary edema in animals cannot help throwing another light on this and related drugs. The mechanism of its pharmacologic action appears not to be entirely explainable on the basis of its antihistaminic properties.

The toxicity of antihistaminic drugs, especially in children, needs clarification. To begin with, the commoner side reactions such as drowsiness, sleepiness, dizziness, headache, insomnia, nervousness, nausea, vomiting, constipation, diarrhea, enterospasm, and dryness of the mouth following ingestion of an antihistaminic agent are the reasons for anxiety. The unusual reactions noted from the antihistaminic drugs in average dosage, such as cardiospasm, urinary retention, allergic symptoms, delirium, narcolepsy, shock-like states and fever, are rare. In our study none of the patients exhibited the unusual side reactions with Phenergan; only five patients found it necessary to discontinue it and another five patients not included in this series did likewise after ingesting only one or two doses. One of these ten patients was a child. This would give a total incidence of 5 per cent of patients who discontinued Phenergan. However, the discontinuance of the drug was necessary in only 2 per cent of the cases. In none of our patients were the side reactions serious, and all disappeared when the drug was stopped. This low incidence of discontinuance of a potent drug like Phenergan is indeed striking, especially in view of its prolonged "antihistaminic" and soporific action.

The real danger from toxicity with any antihistaminic drug is chiefly from accidental overdosage. The statement[4] that children appear to be more susceptible to the antihistaminic drugs than adults applies only to cases of accidental overdosage. The few case reports of children in whom death followed 100 mg of an antihistamine drug have not been convincing. However, deaths can follow the accidental ingestion of from 300 to 1500 mg of an antihistaminic drug. Our experience with Phenergan in the recommended dosage and the proper timing of administration in over 300 patients (193 patients in this report and the remainder from our new series of cases) from two to sixty-seven years of age has revealed it to be not only a valuable but a safe drug to employ for allergic disorders.

It can be unequivocally stated that severe toxicity states from a single daily dose of 25 mg of Phenergan has not been observed by us.

SUMMARY AND CONCLUSIONS

1. Phenergan was employed largely as an adjunctive drug to specific allergy treatment in 193 allergic patients (71 children and 122 adults). The total number of allergy syndromes treated was 351.

2. The drug was ingested usually in a single daily dose of 25 mg before bedtime, for periods ranging from seven to 300 days, the average number of days per patient being sixty-four days.

3. The incidence of therapeutic response for hay fever and perennial allergic rhinitis was higher for children than for adults. The highest response was obtained for cases with urticaria and angioedema. Poor response was observed in asthma, eczema, and neurodermatitis.

4. The incidence of side reactions to Phenergan was significantly lower (35 per cent) and milder for children than for adults (55 per cent). The most common side effect was drowsiness. The removal of the drug was necessary in only 2 per cent of the cases comprising this study.

5. Phenergan compared dose for dose with the other available antihistaminic drugs proved to be the most efficacious and the longest-acting drug.

6. The soporific action of Phenergan makes it an especially desirable antihistaminic agent in allergy practice. Moreover, it is an excellent substitute for the barbiturates when they cause allergy or other symptoms of intolerance.

7. Phenergan has no harmful effects on the blood or blood-forming organs.

8. The statement that children appear to be more susceptible to the antihistaminic drugs than adults applies only to cases of accidental overdosage. Phenergan in the dosage employed is a valuable and safe drug to administer to allergic patients of all ages.

REFERENCES

1. Bain, W. A.; Hellier, F. F.; and Warin, R. P.: Lancet, 257:964, 1948.
2. Bain, W. A., et al: Proc. Roy. Soc. Med., 42:615, 1949.
3. Benacerraf, B., and Fischel, E. E.: Proc. Soc. Exper. Biol. & Med., 71:349, 1949.
4. Editorial Comment, New York State J. Med., 51:1282, 1951.
5. Halpern, B. N.: Compt. rend. Soc. de biol., 140:363, 1946.
6. Halpern, B. N.: J. Allergy, 18:263, 1947.
7. Halpern, B. N.: Personal communication.
8. Halpern, B. N., and Cruchand, S.: Compt. rend. Soc. de biol., 141:1038, 1947.
9. Halpern, B. N., and Ducrot, R.: Compt. rend. Soc. de biol., 140:361, 1946.
10. Halpern, B. N.; Hamburger, P.; and Dubray, C.: Bull. Soc. med. Hosp. Paris, 62:607, 1946.
11. Halpern, B. N., and Martin, J.: Compt. rend. Soc. de biol., 140:830, 1946.
12. Hunter, R. B.: Brit. M. J., 2:169, 1948.
13. Millner, T., and Hurst, A.: Dis. of Chest, 16:870, 1949.
14. Shulman, M. H.: Ann. Allergy, 7:506, 1949.
15. Vallery-Radot, P.; Halpern, B. N., et al: Presse med., 58:661, 1950.
16. Vallery-Radot, P.; Hamburger, P.; and Halpern, B. N.: Presse med., 55:661, 1947.
17. Vallery-Radot, P.; Hamburger, P.; and Halpern, B. N.: Presse med., 55:764, 1946.
18. Waldbott, G. L., and Young, M. I.: J. Allergy, 19:313, 1948.
19. Warin, R. P.: Brit. M. J., 2:169, 1948.

STUDIES ON THE URINARY EXCRETION OF 11-OXYCORTICOSTEROIDS BY ALLERGIC PATIENTS TREATED WITH ADRENOCORTICOTROPIC HORMONE (ACTH)

ALLAN J. STANLEY, PH.D., GEORGE S. BOZALIS, M.D., DICK H. HUFF, M.D., VERNON D. CUSHING, M.D., and LEO CAWLEY, B.S.

Oklahoma City, Oklahoma

A NEW approach to many of the problems of allergy has been made possible by the production of adrenocorticotropic hormone (ACTH) in sufficient quantities for experimental and therapeutic use. The growing literature is evidence of the wide interest in the study of its effects on many different diseases of man.

A preliminary paper by Bordley and co-workers[2] in 1949, along with the publication of the Proceedings of the First Clinical ACTH Conference in February, 1950, containing the papers of Randolph and Rollins[10] and of Rose,[11] as well as the comment of other investigators present at the Conference, gave impetus to the use of ACTH in research on the possible rôle of the pituitary and adrenal glands in asthma of allergic origin. During 1950 the reports of Rose, Paré, Pump and Stanford,[12] of Carey, Harvey, Howard and Winkenwerder,[4] Bordley,[1] Blumenthal,[3] and of Paulsen[9] have added further data on the results of the use of ACTH in intractable asthma. Hioco and Samter[6] have shown that the excretion of urinary 11-oxycorticosteroids by patients with bronchial asthma is essentially within the normal range except when the symptoms have been severe and of long duration, in which case the values are low. The quantity of 17-ketosteroids excreted by these patients was normal.

In this paper we wish to present the clinical observations as well as the chemical determinations of urinary 11-oxycorticosteroids for a series of patients in status asthmaticus who were treated with ACTH.* In all, twenty patients were selected for treatment. They were all in status asthmaticus and did not respond to any type of routine treatment. Their asthma was considered to be of allergic etiology. Table I is a summary of the twenty patients treated with ACTH and the clinical results obtained. Seven brief case histories are presented as typical examples.

Case 1.—Miss R. R., aged fifty-one, was first seen in the clinic April 17, 1950, with a complaint of severe perennial asthma of approximately three years' duration. While

---

Doctor Stanley is associated with the Department of Physiology, University of Oklahoma School of Medicine and University Hospitals.

Doctors Bozalis, Huff, and Cushing, Associate Fellows of The American College of Allergists, are with the Department of Internal Medicine and University Hospitals.

Mr. Cawley is with the University of Oklahoma School of Medicine.

This investigation was supported by a grant from the Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma, in co-operation with the Departments of Physiology and Internal Medicine.

This is Publication No. 11 of the Oklahoma Medical Research Institute.

Approved for publication April 25, 1951.

*Armour brand (Acthar).

TABLE I. CLINICAL SUMMARY OF TWENTY PATIENTS IN STATUS ASTHMATICUS OF ALLERGIC ETIOLOGY TREATED WITH ACTH

No.	Patient	Sex	Age	Type and Duration of Asthma	Total ACTH mg	Clinical Response	Length of Remission	Urinary 11 Oxycorticosteroids
1	R.R.	F	51	Perennial, 3 yrs.	530	Excellent	8 weeks	11 Oxy-corticosteroids not determined — For urinary 11 Oxy-corticosteroids, see Table 2.
2	J.M.H.	M	60	Acute, 2 mos.	365	Excellent	10 days	
					40 wkly. to date	Good	6 weeks*	
3	G.C.I.	M	31	Seasonal, 29 yrs.	200	Excellent	4 weeks	
4	J.D.H.	M	19	Seasonal, 9 yrs.	1st 220	Excellent	5 weeks	
					2nd 220	Excellent	11 weeks*	
5	R.A.M.	M	59	Perennial, 16 yrs.	315	Excellent	16 weeks*	
6	Bev. B.	F	6	Perennial, 2½ yrs.	None	Excellent	12 weeks*	
7	Bee.B.	F	6	Perennial, 5½ yrs.	59	Excellent	14 weeks*	
8	J.C.M.	M	38	Perennial, 35 yrs.	480	Excellent	10 weeks*	
9	O.M.	M	54	Perennial, 8 yrs.	1st 560	Good	3 weeks	
					2nd 500	Good	2 weeks*	
10	N.E.S.	F	56	Perennial, 35 yrs.	525	Good	6 weeks*	
11	H.L.	F	57	Perennial, 12 yrs.	480	Good	4 weeks	
12	W.R.D.	M	61	Perennial, 9 yrs.	400	Poor	None	
13	B.V.	M	19	Perennial, 18 yrs.	235	Good	12 days	
14	H.T.	F	38	Perennial, 15 yrs.	360	Excellent	6 weeks*	
15	E.H.	M	49	Perennial, 5 yrs.	560	Excellent	12 weeks*	
16	L.C.	F	62	Acute, 8 mos.	450	Excellent	4 weeks*	
17	A.F.	F	57	Perennial, 23 yrs.	510	Excellent	4 weeks*	
18	W.E.D.	M	58	Seasonal, 20 yrs.	340	Poor	—	
19	J.H.R.	F	47	Acute, 3 mos.	360	Excellent	4 weeks*	
20	B.H.G.	M	49	Perennial, 35 yrs.	530	Excellent	10 days*	
21	R.N.H.	M	51	Perennial, 21 yrs.	200	Excellent	4 days*	

her asthma was constant more or less the year around, she believes her attacks were more severe during the winter months. The patient's past history was negative except that she had had nasal polyps removed on two occasions. Both times the local anesthetic which was used gave her some asthma.

She was placed on routine therapy, including iodides and the aminophylline and ephedrine drugs for p.r.n. use. In addition, she was given deep x-ray therapy and was started on a program of desensitization, including house dust and ragweeds. Her condition improved remarkably, and she remained well for a period of about one month. After having surgery for removal of some more nasal polyps, she once again developed the symptoms of asthma which were so severe that she required constant therapy and medication, including oxygen by inhalation.

She was hospitalized August 1, 1950, and was placed on ACTH; she received a total of 530 mg over a period of nine days. Three days after the ACTH therapy was started, there was a marked improvement in her condition and she was up, requiring no medication. She developed a transitory glycosuria and slight edema of the face and lower limbs, and a mild acneiform eruption appeared on her trunk and lower extremities persisting for two months. Her desensitization program was continued, and the patient remained free of any asthma for a period of about two months. Since then she has had two severe attacks of asthma approximately two months apart.

Case 2.—Mr. J. M. H., aged sixty, was first seen in the clinic December 1, 1948, with a history of asthma of two months' duration. He gave a history of chronic sinusitis of several years' duration. He was started on desensitization and symptomatic therapy and responded well, remaining free of any asthma until June, 1949, at which time he had some mild recurrence of his asthma. However, he remained fairly well until October, 1949, at which time he had another attack of asthma associated with an upper respiratory infection, and once again in March, 1950, he had an attack of asthma which responded well to symptomatic therapy.

In September, 1950, his asthma became more severe and would not respond to any type of therapy; he was hospitalized and was given a total of 365 mg ACTH over a period of nine days. His response to ACTH was excellent, and his symptoms of asthma cleared completely. He developed a glycosuria, +2, and edema of the face,

with signs of free fluid in the abdomen. These symptoms disappeared promptly and he remained free of any difficulty for a period of about ten days, at which time because of recurrence of asthmatic symptoms he was placed on a maintenance dosage of ACTH, 20 mg twice weekly.

He has remained on this maintenance dosage for a period of six weeks and has remained free of any asthma. No untoward reaction has been observed from the use of this maintenance dose of ACTH.

Case 3.—Mr. G. C. L., aged thirty-one, was first seen in the clinic October 2, 1950, with a history of seasonal asthma since infancy. Asthma for the greater part would come on in the late summer and fall and would last until about the first frost.

At the time the patient was first seen, he was having some mild asthma which during the course of investigation became more severe. The patient finally went into status asthmaticus and was immediately hospitalized. He did not respond to any routine therapy, and consequently ACTH was started. He received a total of 200 mg of ACTH over a period of five days. His response to ACTH was excellent, and at the time of discharge from the hospital he was free from asthma.

The patient was then placed on routine desensitization and was given other symptomatic therapy, including iodides and ephedrine and aminophylline drugs by mouth for p.r.n. use. He remained free of any asthma for approximately one month, at which time he had a severe asthmatic attack, but he was treated successfully on this occasion at home with the use of aminophylline intravenously and epinephrine hypodermic injection. Since then his general condition has been good, and he has been free of asthma to date.

Case 4.—Mr. J. D. H., nineteen years old, white, was first seen in the clinic on August 25, 1949, with a history of asthma, seasonal in character, of nine years' duration. For the greater part, his asthma would be in the late summer and fall. He was treated symptomatically and was desensitized with antigens of house dust, Alternaria, Fusarium, ragweeds, and the amaranths.

During the summer and fall of 1949, his condition was excellent. In August, 1950, the patient had an acute attack of asthma and did not respond to any therapy tried. He was hospitalized in September, 1950, and was given a total of 220 mg of ACTH over a period of five days with an excellent clinical response.

He remained free of any asthma for a period of approximately five weeks, at which time he once again went into status asthmaticus following an upper respiratory infection. He was given ACTH on the second occasion in the amount of 220 mg over a period of six days. His second response to ACTH was also excellent, and the patient has been free of any asthma since the last course. He has remained on the desensitization program mentioned above. Vital capacity was 3.8 liters or 83 per cent of normal after the second course of ACTH.

Case 5.—Mr. R. A. M., aged fifty-nine, white, male, was first seen in the clinic August 16, 1948. He gave a history of chronic bronchial asthma, perennial in type, of approximately sixteen years' duration. For two years prior to coming to the clinic, his asthma had become progressively more severe. He was placed on a desensitization program using pollen and dust therapy and was given symptomatic treatment in the form of iodides and relaxant drugs.

In October, 1950, he was seen again and at that time had been having nearly constant asthma for a period of several weeks. This asthma did not respond to any therapy or treatment given. He was hospitalized and a total of 315 mg of ACTH was given over a period of one week. His clinical response to ACTH therapy was excellent, and he has remained free of any asthma to date.

The vital capacity prior to the ACTH therapy was 3.0 liters or 70 per cent of

normal; after ACTH therapy, the vital capacity was 3.6 liters or 83 per cent of normal.

Case 6.—Miss Beverly B., aged six, was first seen in the clinic on July 13, 1948. She gave a history of asthma of approximately two-and-a-half years' duration. The asthma apparently has been perennial in type.

She was found to be quite sensitive to several foods as well as to house dust and molds. Desensitization consisted of house dust with molds and she was also given a stock streptococcic-staphylococcic vaccine. Her response to symptomatic therapy was very poor, and she continued to have nearly constant asthma.

She was hospitalized and it was planned to give ACTH; however, during the preliminary observation period during which time twenty-four-hour specimens of urine were being collected, the patient's condition rapidly improved and her symptoms of asthma disappeared. She was kept in the hospital over a period of six days, and urinary 11-oxycorticosteroids were determined daily.

The desensitization program has been maintained, and the patient has remained free of asthma to date.

Case 7.—Miss Becky B., aged six, was first seen in the clinic May 24, 1946, with a history of asthma since the age of eighteen months. The original attack came on following a severe upper respiratory infection.

She was placed on a program of desensitization, and certain foods were eliminated from her diet. In addition, she was treated symptomatically with various aminophylline and ephedrine compounds.

She continued to have frequent attacks of asthma in spite of any therapy, and in mid-1950, her asthma became quite severe and would not respond to any type of therapy.

In October, 1950, the patient was hospitalized and received a total of 59 mg of ACTH over a period of five days. Her clinical response to the ACTH was excellent, and she has remained practically free of any asthma.

11-OXYCORTICOSTEROID DETERMINATIONS

Of the twenty patients treated with ACTH, urinary 11-oxycorticosteroid determinations were made for twelve and for one control patient who did respond to routine treatment. All patients but one were hospitalized, and a twenty-four-hour urine sample was collected before ACTH was given. The 11-oxycorticosteroids were determined, using the pretreatment urine specimen as a control for daily samples, and determinations were made during the course of treatments with ACTH. Each patient thus served to this extent as his own control. A longer pretreatment control period would be desirable, but the condition of the patients did not permit of any additional delay. The patients were then given various doses of ACTH, never exceeding more than 20 mg every six hours until a clinical response was obtained. The doses were then reduced. Other symptomatic measures were prescribed as needed during the early part of the course of ACTH therapy. The 11-oxycorticosteroids were determined by the method of Corcoran and Page[5] with minor modifications by Mason.[7] This method, making use of periodic acid oxidation, is highly consistent in results obtained and is in general use for quantitative determination of formaldehydogenic compounds.

The patients were seen daily by at least one of the authors. The nurses in attendance were carefully instructed as to the importance of collecting a complete twenty-four-hour specimen of urine. The specimens were collected from 6:00 A.M. to 6:00 A.M. daily and brought to the laboratory promptly for processing. Table II is a summary of the 11-oxycorticosteroid determinations obtained on these thirteen patients.

Careful study of these results shows that there is no correlation between the dosage of ACTH used in these cases and the quantity of urinary 11-oxycorticosteroids excreted. Each individual in all cases but two, however, had a higher excretory rate of 11-oxycorticosteroids while receiving ACTH than when not receiving it. These results are similar to those of Sprechler,[13] who made determinations on twenty-five patients suffering from various diseases other than asthma while on ACTH medication. The variation between individuals is striking, ranging from one fifth to five times the control levels on the day of greatest excretion of 11-oxycorticosteroids. In one patient, Case J. D. H. (Table II), who received two courses of ACTH, the second maximal response did not occur until three days after cessation of ACTH administration. One six-year-old patient, Becky B., responded to small doses of ACTH very satisfactorily. Paulsen[9] has called attention to a few young children who did not respond well.

The relief of symptoms began within twenty-four to forty-eight hours in all cases and was characterized by relaxation, an increase in feeling of well-being, greater ease in breathing, and a marked reduction in coughing and production of mucus. The diminished sputum became more fluid in consistency and clearer in color. Practically all of the above observations have been made also by the authors cited in the early part of this paper.

The urinary output at this time was usually decreased, by as much as a third to a half in some cases. The skin became moist, indicating an increase in hydration as a result of the water retention. Within ninety-six hours the râles and wheezes had disappeared. In two cases, W. R. D. and W. E. D. (Table I), who gave a poor clinical response, the underlying emphysema which was marked in both patients probably accounts for the lack of satisfactory improvement. W. R. D. (Table II), had an average response in 11-oxycorticosteroids and showed other minor improvement. In only two cases was there any noticeable edema. In two patients, Cases R. R. and J. M. H. (Table II), some facial and pedal edema developed but regressed satisfactorily upon cessation of ACTH administration. Here also, it will be noted that those two patients excreted more 11-oxycorticosteroids than any of the other ten for whom they were determined. In the dosage used in this series of cases there was no evidence of decreased glucose tolerance or any suggestion of permanent disturbance in glucose metabolism. In the patients who had glycosuria, the glucose tolerance curves were normal. These patients exhibited a transient glycosuria which disappeared after ACTH was discontinued. The only other untoward reaction occurred in the case of R. R., who developed a mild acneiform eruption on the trunk

TABLE II. EFFECT OF INTRAMUSCULAR INJECTION OF ADRENOCORTICOTROPIC HORMONE (ACTH) ON THE EXCRETION OF URINARY 11-OXYCORTICOSTEROIDS IN PATIENTS IN STATUS ASTHMATICUS

Patient No.	Day	ACTH, mg Administered Per Day	11-Oxycorticosteroids mg Excreted Per 24 Hours	Patient No.	Day	ACTH, mg Administered Per Day	11-Oxycorticosteroids mg Excreted Per 24 Hours
1	Control	None	1.59	2	Control	None	0.51
R.R.	1	40	—	J.M.H.	1	40	1.35
Female	2	80	0.74	Male	2	80	—
Age 51	3	80	1.32	Age 60	3	80	0.92
	4	80	2.66		4	65	2.47
	5	80	5.55		5	20	1.66
Univ.	6	70	5.78	Univ.	6	20	1.21
Hosp.	7	40	—	Hosp.	7	20	—
164570	8	20	2.02	166514	8	20	0.79
	9	None	0.16		9	20	0.45
	10	None	0.97		10	None	0.27
	13	None	0.67		11	None	0.87
	15	None	0.15		12	None	1.39
	16	None	0.32		13	None	0.99
	18	None	0.19		14	None	0.58
	26	None	0.27		52	None	0.14
	37	None	0.32				
3	Control	None	1.32	4	Control	None	0.37
G.C.I.	1	60	—	J.D.H.	1	80	—
Male	2	50	0.35	Male	2	80	0.60
Age 31	3	40	—	Age 19	3	40	0.63
	4	40	0.27		4	20	—
	5	10	0.13				
Wesley	6	None	0.29	Second course 30 days later			
Hosp.	7	None	0.11				
H-43699	8	None	—	St.	Control	None	0.20
	9	None	0.11	Anthony's	1	80	0.26
				Hosp.	2	80	0.31
				234871	3	20	0.39
					4	20	0.10
					5	20	0.20
					6	None	—
					7	None	0.06
					8	None	0.67
					9	None	—
					10	None	0.27
					11	None	0.20
5	Control	None	0.13	6	1	None	0.23
R.A.M.	1	40	—	Beverly B.	2	None	0.22
Male	2	80	0.44	Female	3	None	0.30
Age 60	3	75	0.27	Age 6	4	None	0.33
	4	40	0.26		5	None	—
Univ.	5	20	—	St.	6	None	0.19
Hosp.	6	20	0.47	Anthony's	7	None	0.29
166875	7	20	—	Hosp.			
	8	20	0.25	246000			
	9	None	—				
	10	None	0.49				
7	Control	None	0.18	8	1	40	—
Becky B.	1	10	—	J.C.M.	2	80	0.46
Female	2	20	0.33	Male	3	80	0.25
Age 6	3	14	—	Age 38	4	80	0.31
	4	12	0.56		5	160	0.40
St.	5	3	0.47	St.	6	80	—
Anthony's				Anthony's	7	80	0.19
Hosp.				Hosp.	8	80	0.29
196685				248515	9	60	0.65
9	Control	None	0.34	10	Control	None	0.58
O.M.	1	80	0.27	N.E.S.	1	40	—
Male	2	80	0.57	Female	2	80	0.28
Age 54	3	80	0.60	Age 56	3	80	0.35
	4	80	0.45		4	100	0.16
Univ.	5	80	0.59	Mercy	5	80	0.25
Hosp.	6	60	0.66	Hosp.	6	70	0.13
164856	7	40	0.77	93136	7	35	—
	8	20	0.49		8	20	—
	9	20	0.40		9	20	—
	10	20	0.51				

TABLE II. *(Continued)*

Patient No.	Day	ACTH, mg Administered Per Day	11-Oxycorticosteroids mg Excreted Per 24 Hours	Patient No.	Day	ACTH, mg Administered Per Day	11-Oxycorticosteroids mg Excreted Per 24 Hours
11	Control	None	0.34	12	Control	None	0.22
H.L.	1	80	—	W.R.D.	1	80	—
Female	2	80	0.78	Male	2	80	0.90
Age 57	3	80	0.77	Age 61	3	80	0.58
	4	40	0.71	Not	4	80	0.57
St.	5	40	0.81	Hosp.	5	80	0.41
Anthony's	6	40	0.78				
Hosp.	7	20	0.77	13	1	20	0.68
240222	8	20	0.44	B.V.	2	80	0.43
	9	20	—	Male	3	75	0.24
	10	10	0.66	Age 19	4	60	0.86
				Univ. Hosp. 167670			

and lower extremities. This is the only patient who might be said to have developed a sensitivity to the preparation.

Several possibilities might be considered in the case of those individuals who failed to show an increased excretion of 11-oxycorticosteroids while receiving ACTH.

1. Their adrenal cortices might not have been sufficiently responsive to ACTH in the dosage used to produce any excess beyond metabolic needs.
2. Their utilization of adrenal steroids might have been more complete due to factors unknown.
3. Their adrenal cortices might have been at the end of an exhaustive phase due to the severe attack of asthma which had existed for some time before ACTH was given. Their prompt clinical response would seem to make the first two possibilities more acceptable.

The other two exceptional cases in this series are those with high excretion rates of 11-oxycorticosteroids (R. R. and J. M. H., Table II). While no direct evidence is at hand by way of an explanation, the possibility of other disturbed physiology such as liver damage should not be overlooked. Such a condition, though not apparent at this time, might conceivably bring on the greater elimination of these hormones because the mechanism for their more complete utilization had been interfered with.

The excretion curves for the other eight patients lie easily within normal range when compared with those of normal healthy persons receiving similar amounts of ACTH.[8] The wide variations in control values in this series and in those of other authors[6,9,13] make it difficult to evaluate the excretion of 11-oxycorticosteroids as a measure of adrenal stimulation by the dosage used.

VITAL CAPACITY DETERMINATIONS

It became apparent during the course of this investigation that vital capacity determinations made prior to the administration of ACTH and again after the symptoms of status asthmaticus had subsided could be con-

sidered an important objective measurement of the physiological state of pulmonary function. Many elderly asthmatic patients have an underlying emphysema which limits their vital capacity to less than 50 per cent of normal. Any further reduction such as that superimposed by an asthmatic attack can effectively place the patient in critical need of additional gas exchange. Vital capacity determinations, made at the time of cessation of symptoms of asthma, can be of use in determining the amount of emphysema, which has been considered up to now to be irreversible. Such determinations were made on seven patients of this series, and the results are given in Table III.

TABLE III. THE EFFECTS OF ACTH ON VITAL CAPACITY IN PATIENTS IN STATUS ASTHMATICUS

Case	Vital Capacity in % of Normal	
	Before ACTH	After ACTH
R.A.M.	70	83
N.E.S.	42	64
W.R.D.	37	56
J.D.H.	44	83
J.M.H.	77	106
R.R.	28	100
G.C.I.	55	114
Average	50+	86+

When ACTH is given, the mucus plugs are seemingly dissolved. The lung fields become clear in the absence of cough, and the quantity of sputum is reduced to a mere fraction of that produced prior to ACTH administration.[9] The tremendous reduction in energy requirements for the act of breathing enables the patient to relax and rest, a fact of no little importance in the recovery process. A series of charts is presented in order to show graphically the quantity of 11-oxycorticosteroids excreted daily and the change in vital capacity which occurs as a result of ACTH administration.

SUMMARY

1. Complete cessation of symptoms of status asthmaticus resulted in eighteen of twenty patients treated with adrenocorticotropic hormone (Acthar, Armour) within six days. Subjective improvement occurred in twenty-four to forty-eight hours, and marked objective improvement occurred in forty-eight to ninety-six hours.

2. Chemical determinations of the urinary 11-oxycorticosteroids of twelve patients who received ACTH and of one who did not, were made during the course of treatment and are shown together with the daily doses of ACTH. The quantitative excretion of 11-oxycorticosteroids does not parallel either the dose of ACTH or the clinical response.

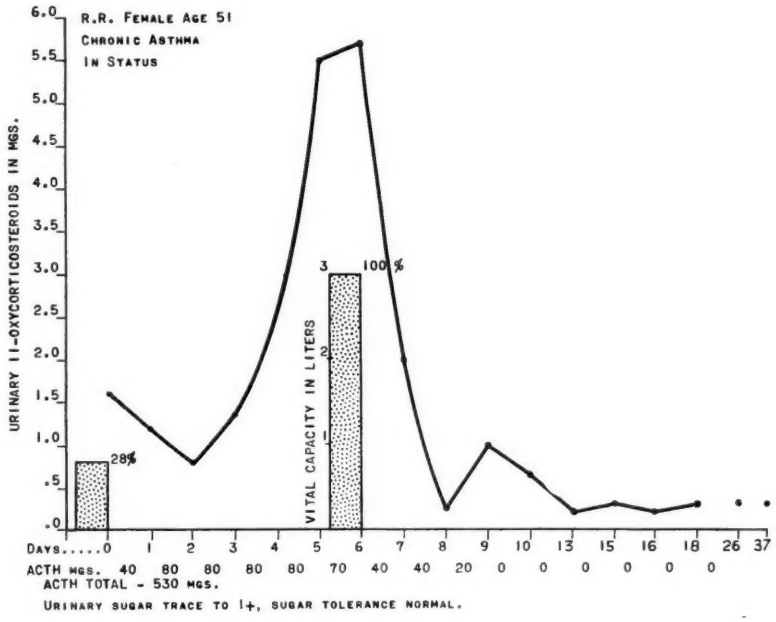

Chart I.

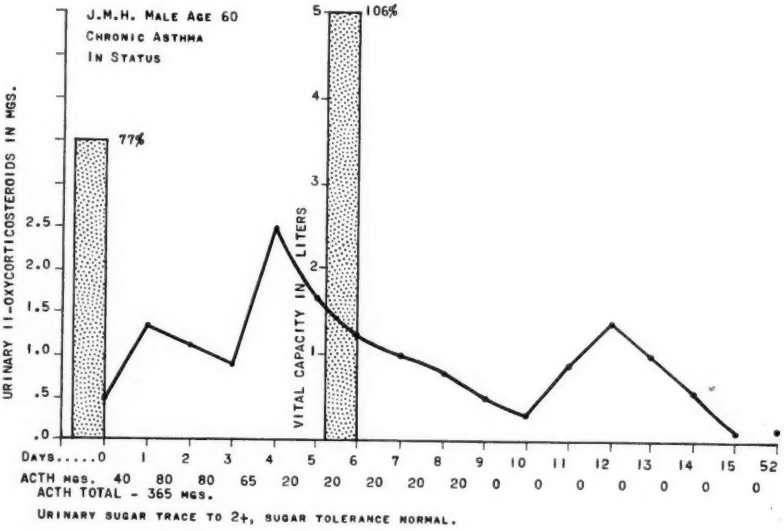

Chart II.

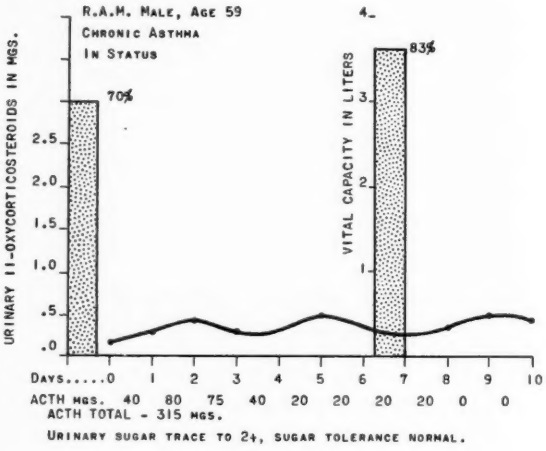

Chart III.

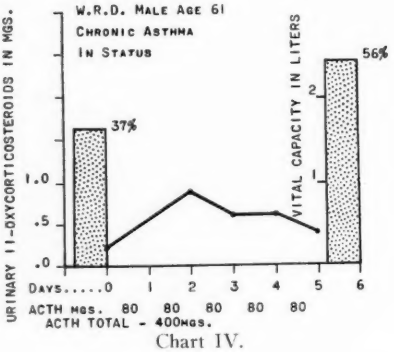

Chart IV.

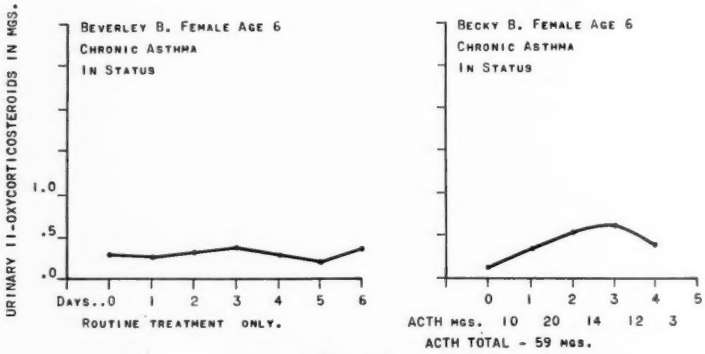

Chart V.

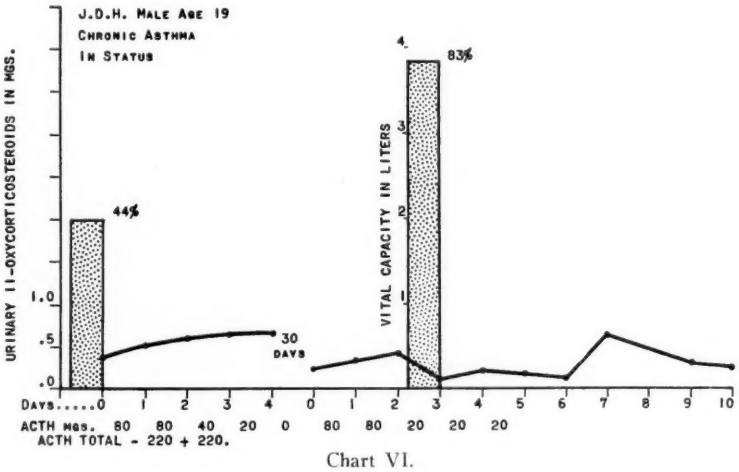

Chart VI.

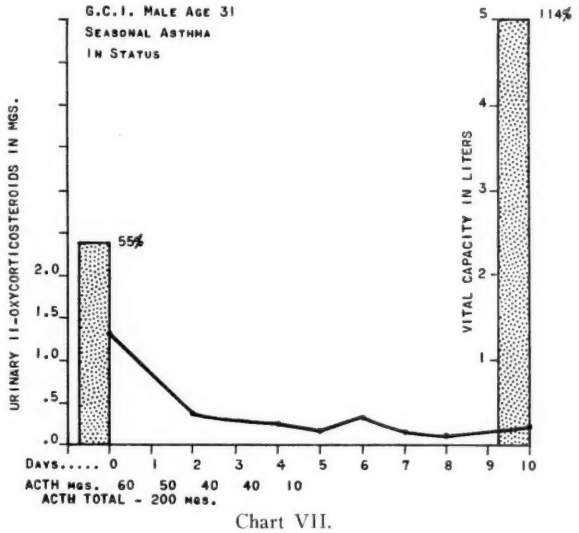

Chart VII.

3. Two types of excretion curves of 11-oxycorticosteroids are apparent in this series. One is characterized by a marked increase, the second by little or no change beyond a slight day to day variation.

4. In all patients tested there was an increase in vital capacity coincidental with the relief of other symptoms amounting on the average in seven patients to 36 per cent of their normal vital capacity. These determinations can assist in evaluating the permanent pathology present.

CHARTS

The series of charts shown is made from data contained in Tables II and III. 0 day in each case is the control determination. The other numbers represent days after the start of ACTH administration.

BIBLIOGRAPHY

1. Bordley, J. E.: Observations on changes taking place in the upper respiratory tract of patients under ACTH and cortisone therapy. Bull. Johns Hopkins Hosp., 87:415, 1950.
2. Bordley, J. E.; Carey, R. A.; Harvey, A. M.; Howard, J. E.; Kattus, A. A.; Newman, E. V.; and Winkenwerder, W. L.: Preliminary observations on the effect of adrenocorticotrophic hormone (ACTH) in allergic diseases. Bull. Johns Hopkins Hosp., 85:396, 1949.
3. Blumenthal, J. S.: Pituitary adrenocorticotrophic hormone (ACTH) in asthma. Minnesota Med., 33:797, 1950.
4. Carey, R. A.; Harvey, A. M.; Howard, J. E.; and Winkenwerder, W. L.: The effect of adrenocorticotrophic hormone (ACTH) and cortisone on the course of bronchial asthma. Bull. Johns Hopkins Hosp., 87:387, 1950.
5. Corcoran, A. C., and Page, I. H.: Methods for the chemical determination of corticosteroids in urine and plasma. J. Lab. & Clin. Med., 33:1326, 1948.
6. Hioco, D., and Samter, M.: The excretion of 17-ketosteroids, 11-oxycorticosteroids and "11-desoxycorticosteroids" in patients with bronchial asthma. J. Clin. Endocrinol., 10:1570, 1950.
7. Mason, H. L.: Personal communication.
8. Mason, H. L.; Power, M. H.; Rynearson, E. H.; Ciaramelli, L. C.; Li, C. H.; and Evans, H. M.: Results of administration of anterior pituitary adrenocorticotrophic hormone to a normal human subject. J. Clin. Endocrinol., 8:1-14, 1948.
9. Paulsen, F.: Pharmacological and clinical results with ACTH in 112 cases. Acta Endocrinol., 5:292, 1950.
10. Randolph, T. G., and Rollins, J. P.: Relief of allergic diseases by ACTH therapy. Proceedings of the First Clinical ACTH Conference. Philadelphia: The Blakiston Co., 1950.
11. Rose, Bram: Studies on the effect of ACTH on eosinophilia and bronchial asthma. Proceedings of the First Clinical ACTH Conference. Philadelphia: The Blakiston Co., 1950.
12. Rose, Bram; Pare, J. A. P.; Pump, K.; and Stanford, R. L.: Preliminary report on adrenocorticotrophic hormone (ACTH) in asthma. Canad. M. A. J., 62:6, 1950.
13. Sprechler, M.: Investigations on the urinary excretion of corticoids and 17-ketosteroids during the administration of adrenocorticotrophic hormone (ACTH). Acta Endocrinol., 5:101, 1950.

COLLEGE-SPONSORED BOOK WELL RECEIVED

Allergy in Relation to Pediatrics by Bret Ratner, M.D., and sixteen other well-qualified pediatric allergists, and sponsored by The American College of Allergists, has met with unusual success. It has been necessary to reprint the book. *California Medicine*, in its November, 1951, issue, presents a favorable review, stating, "This book is invaluable to the pediatrician, for it is a well-recognized fact that he is dealing with allergic conditions in from 30 to 50 per cent of his patients, depending on the locale in which he is practicing. The contents include specialized knowledge of the fundamentals of allergy, and present well-organized discussions on accepted methods of investigation and treatment. . . . The volume is extraordinarily useful due to the splendid bibliography prepared by each contributor."

Another thousand copies have been made available. If you have not obtained your copy, do so now, as there will not be another printing. The price is $3.75. Place orders directly with Bruce Publishing Company, 2642 University Avenue, St. Paul 4, Minnesota.

ENDOCRINE HYPERSENSITIVITY

LEONARD MELTZER, M.D.
Houston, Texas

As early as 1916 it was suspected that the abnormal functioning of endocrine glands might be reflected in the guise of cutaneous disorders. Earliest among these changes noted was that of the thyroid gland which resulted in localized cutaneous myxedema. However, it was not until 1945 that the concept of hypersensitivity to endocrines was advanced by Zondek and Bromberg.[9] They were initially interested in hypersensitivity and refractoriness to insulin. In 1947[10] they published additional reports on this subject, including hypersensitivity to endocrines other than insulin. They performed control tests on random samples of the population which seemed to prove that endocrine skin tests were positive only in persons with some endocrine disturbance. Normal subjects, that is, persons with no apparent endocrine disturbance, would at no time give positive skin tests to endocrine test materials. The thought immediately arises as to why an individual who has this hypersensitivity does not have the reaction at all times, since most endocrines are present in the blood stream at all times in varying amounts. A notable exception to this constancy is that of progesterone in the female. Case histories and the discussion which follows will tend to prove that there is necessary a certain circulating blood level for a reaction to be elicited in some cases, just as quantitative factors are important in allergy to food or inhalants.

Zondek and Bromberg[9] and later Baer and Witten[1] not only were able to demonstrate such hypersensitivity by intradermal test, but were also successful in desensitizing a fair percentage of such hypersensitized individuals. Although it may be argued that the normal rising and falling titer of such endocrines in the blood stream should accomplish desensitization, the fact remains that frequent parenteral introduction of increasing doses has accomplished what the body has apparently not been able to do. That supposedly minute doses, by the parenteral route, may act as a trigger mechanism is evident from the case of Mrs. A. H.

It is pretty generally accepted that endocrines play a considerable role in acne vulgaris, especially during adolescence. Lawrence and Werthussen[6] proposed the theory in 1942 that a disturbance in the balance between androgens and estrogens caused the eruption. Hamilton[4] further suggested that the relative preponderance of androgens caused the acne. The introduction of testosterone into the blood stream supposedly stimulates the sebaceous glands to increased activity. This, along with congenitally inadequate sebaceous gland ostia and dietary and hygienic factors, produces acne. In the female adolescent the onset of menses introduces progesterone

Approved for publication August 14, 1951.

into the blood stream. The close similarity of the organic formulas of progesterone and testosterone is certainly very striking (Fig. 1).

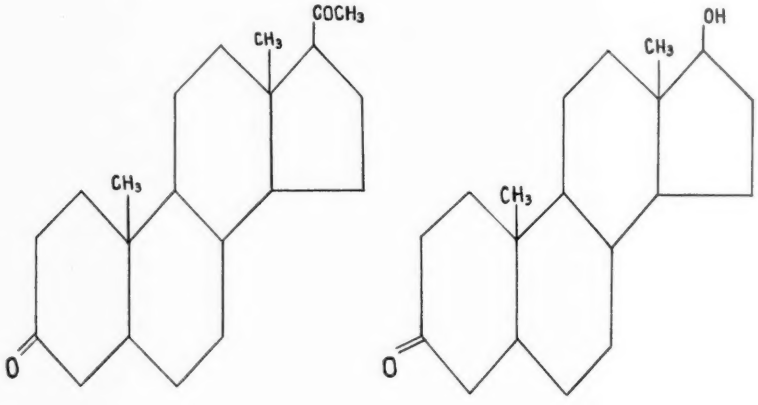

Fig. 1.

Grollman[3] states that ethinyl testosterone has some progesterone-like activity, amounting to one-third of the biological effect. Why should not progesterone have a testosterone-like effect on the sebaceous glands? The monthly exacerbations noted in adolescent females occur usually during the week immediately preceding menstruation. This is exactly the time when the progesterone level reaches its peak. Of further interest is Goeckermann's report that acne in girls does respond to administration of estrone or estrone-like substances.[2] He supports my suggestion of the quantitative principle by stating that the dosage was individualized depending on the clinical response. Unfortunately, he does not state why he considered twenty-six cases, which he selected for therapy, as suitable for endocrines. I cannot understand his expecting male patients to improve with testosterone, since it is agreed that it stimulates sebaceous secretion. Belisario in discussing this work of Goeckermann confirmed this author's impression by stating that in his hands males did as well on estrogen therapy. The probable similarity in the action of progesterone and testosterone would also explain those cases of continued acne in women in their late twenties and even into their thirties who have premenstrual flares and do not manifest sensitivity to the endocrines by skin test. Urbach[7] felt that these premenstrual flares were due to an endogenous allergen. Way and Andrews,[8] in their excellent study of 145 women with acne, deny the possibility of allergy as a factor. This author cannot agree that their

patients were adequately investigated for allergy, since no skin tests were performed. Their administration of progesterone with good or bad results does not prove or disprove the allergic factor. Further, their feeling that because estrone and progesterone are both at low levels when exacerbations do occur, the endocrine factor is not important, is not valid. It must be kept in mind that, of necessity, there is a lag between the peak level in the blood and reaction in the skin. Hooker and Pfeiffer[5] suggested that the improvement following estrogen therapy in acne was probably due to this inhibitory effect on the sebaceous glands.

Stimulated by some of the earlier work and having the impression that there are other dermatoses and diseases with a rhythmic recurrence which might well be founded on a hypersensitivity, the author collected the data presented in Table I.

It had originally been intended to use Helvetian olive oil, as suggested by Zondek and Bromberg. Because of the difficulty in obtaining this and because the majority of American endocrine preparations are suspended in peanut or sesame oil, the former was substituted. Estrone, estradiol, progestin, testosterone, cortate, and cholesterol were added in concentration of 1 mg per cc to U.S.P. peanut oil and the solutions cleared. The tests were performed by injecting 0.1 cc, which is equivalent to 0.1 mg of the endocrine, slightly deeper than intradermally. In the course of testing females who were menstruants, it was discovered that the test results varied depending on the phase of the menstrual cycle. Women on whom tests were negative during the first ten days of the cycle would give positive tests from the twelfth to fourteenth and twenty-second to twenty-fifth days. The modern concepts of estrogen levels indicate the reasons for these phenomena. According to these concepts there are three elevations of the estrone level during the normal menstrual cycle. The first increase occurs about the second postmenstrual day and lasts until the fifth. The rise is moderate. The second rise starts about the ninth day, reaches a maximum at the twelfth and gradually drops around the seventeenth day. There follows a third rise which reaches its height on the twenty-first to twenty-second day and drops back to normal level by the twenty-fifth or twenty-sixth day.

Progesterone appears in the blood following ovulation around the fourteenth day and reaches a maximum around the twenty-second day, gradually disappearing by the end of the cycle. This latter is important and has not received enough attention from the endocrinologists or the dermatologists in its relation to acne vulgaris. This late rise would account for the premenstrual flares in many cases of female adolescent acne.

Four cases warranted an attempt at desensitization, and the history of three is given in some detail below.

Case 1.—W. O. D., a thirty-nine-year-old white woman, who at the age of thirty-five had had a complete hysterectomy and bilateral salpingo-oophorectomy, was started

TABLE I

Case	Sex	Age	Clinical Diagnosis	Duration	Reaction to Test								Remarks
					1	2	3	4	5	6	7	8	
H.J.	F	28	Acne vulg.	8 yrs.	0	+	0	0	++	0	0	+	First test 5 days pre-ovulat.
					0	0	++	0	0	0	0	0	Second test 25th day of cycle
S.M.	F	33	Acne vulg.	3 yrs.	0	0	0	0	0	0	0	++	Second test on 25th day of cycle
					0	0	0	0	+	0	0	0	
S.H.	F	29	Urticaria pigmentosum	6 yrs.	0	0	0	0	0	+	0	+	Diagnosis proven by biopsy
B.D.	F	27	Acne vulg., urticaria	4 yrs.	0	0	+++	+++	0	0	0	0	Unilat. oophorectomy prior to onset of symptoms
S.C.	F	20	Acne vulg.	8 yrs.	0	0	+++	+++	0	0	0	0	Dysmenorrhea
L.S.	M	65	Urticaria, chronic	10 yrs.	+	+++	0	+	+	+	0	+	Improved on low cholesterol diet
W.O.D.	F	39	Dermatitis medicam.	4 yrs.	0	0	+++	0	+	0	0	0	Hysterectomy and bilateral salpingo-oophorectomy
B.K.	F	41	Recurrent telangiect.	1 yr.	0	0	+++	0	0	0	0	0	Hysterectomy and bilateral salpingo-oophorectomy
J.T.	F	23	Acne vulg.	9 yrs.	0	0	0	++	0	0	0	0	
					0	0	0	0	++	++	0	0	
J.S.	F	35	Chronic urethritis	3 yrs.	0	0	+	0	0	+	0	0	
A.H.	F	29	Vesicular, erup., hands	15 yrs.	0	0	+++	++	0	0	0	0	Started as swelling of hands at onset of menses
J.K.	F	34	Hyperkeratosis, hands	9 yrs.	0	0	++	++	0	0	0	0	Very marked improvement after three months treatment
R.H.	F	28	Acne vulg., urtic., scl.	7 yrs.	0	0	++	++	0	+	0	+++	Improved on Premarin
G.L.	F	35	Acne vulg. atopic derm.	20 yrs.	0	0	+++	+	0	0	0	+	Cleared without desensitization
M.C.	F	18	Acne vulg.	7 yrs.	0	0	0	+	+++	0	0	0	Improvement on ovarian extract
J.B.	F	26	Chr. ureth.	3 yrs.	0	0	+++	0	0	0	0	0	Relieved by antihistamines
E.J.	F	54	Seborrhea	3 mos.	0	0	0	++	0	0	0	0	Menopause, 1949

Key to testing materials:
1—Peanut oil
2—Cholesterol in peanut oil
3—Esterone in peanut oil
4—Estradiol in peanut oil
5—Progestin in peanut oil
6—Testosterone in peanut oil
7—Androsterone in peanut oil
8—Cortate in peanut oil
Solutions prepared by the Ciba Pharmaceutical Company.

on theelin injections two months after operation, because of the onset of menopausal symptoms. After three or four months of this substitution therapy, she noticed severe itching on her forearms and cubital areas and the appearance of a papular eruption which would subside almost completely, only to be reactivated by the next injection. Under local therapy and sedation and withholding of all endocrines, the rash subsided within ten days. At that time intradermal tests were performed and resulted in markedly positive reactions to estrone and progestin.

The patient was started on tri-weekly injections of a mixture of these two endocrines in concentration of 0.1 mg per cc. The initial dose was 0.1 cc of this concentration, which would be equivalent to 0.01 mg. This minute amount was sufficient to cause pruritus on the previously involved areas. The dose was repeated three times. When the dose had reached 1.0 cc, the solution was changed to one containing 1 mg per cc and the injections again started with 0.1 cc. By the time that the dosage had reached 0.3 cc of this new concentration, there was a definite eruption in the old areas of involvement accompanied by considerable pruritus. The attempted desensitization was stopped because it was obviously not succeeding. Now eighteen months later the patient reports that her menopausal symptoms require estrogen substitution about twice each month. Her dermatitis recurs following each injection. This seems to be a definite case of dermatitis medicamentosum to two endocrines brought on by exogenous introduction.

Case 2.—B. D., a twenty-seven-year-old white woman, who about five years previously has had a unilateral oophorectomy performed because of a cystic ovary, one year postoperatively developed a moderate acneform eruption on her face and body with postmenstrual flares. This was accompanied by migraine-like headaches and vomiting. Endocrine skin tests revealed a marked reaction to both estrone and estradiol. When they had subsided after two weeks, the patient was given 1 mg of estrone and estradiol intramuscularly. Within twelve hours this caused a flare of the previously positive test sites. With this corroborative evidence desensitization was begun. The initial dose was 0.01 mg of estrone and estradiol, started on November 21, 1949. By January 21, 1950, the dose had been increased to 0.3 mg. The severity of the symptoms had decreased, especially of the headaches. It was noticed that the complex of symptoms developed sometime after the eighth postmenstrual day. This is apparently an endogenous sensitivity with a definite quantitative factor, because some time near the ovulatory period these endocrines have reached a level sufficient to elicit symptoms. This led to some interesting observations and speculation. Bimonthly flares were noticed in other acne cases in women, and the author believes such cases are due to estrone hypersensitivity.

Case 3.—B. K., a forty-one-year-old white woman, gravida II, para I, had had a hysterectomy and bilateral salpingo-oophorectomy performed in 1946 because of uterine fibroids. She was started on weekly injections of theelin in oil as substitution therapy. In 1947, after approximately one year of this treatment, it was noticed that tender, painful, telangiectatic areas developed on the lower trunk and extremities at intervals of twenty-eight to thirty-two days. Various blood studies including bleeding, clotting, and prothrombin time were normal. Endocrine skin tests revealed a markedly positive reaction to estrone. After this test had subsided, a recurrent test performed by intramuscular injection of 1 cc of estrone caused a flare in the old test site. Attempted desensitization was decided upon, starting with .01 mg and increasing the dosage daily. After sixty daily injections had been administered, no further telangiectases appeared. Since then the patient has received one injection of estrone every two weeks and has had no recurrence of symptoms.

TABLE II. ACNE CASES

Duration of symptoms	3 to 9 years
Positive to estrone	3 cases
Positive to estradiol	7 cases
Positive to estrone and estradiol	3 cases
Positive to progesterone	4 cases
Positive to testosterone	2 cases
Positive to testosterone and progesterone	2 cases
Negative to all	0 cases
One flare per month	4 cases
Two flares per month	2 cases

The problem immediately presents itself as to how a castrate can be sensitive to ovarian extract. Two explanations are possible. First, we must consider that reagin was formed by introduction of an allergen, theelin in oil. It can further be postulated that such reagin continues to be produced even when injections are no longer given to the patient. Secondly, Grollman and other endocrinologists agree that the hypophysis secretes a gonadotropic factor among which is a follicle-stimulating one. Moreover, it has been proven that the hypophysis of the castrate hypertrophies and increases the secretion of F.S.H. This would, in part, explain the continued flares even without substitution therapy.[3]

Of the ten patients tested who did not suffer from acne, two merit some discussion because of their implications.

A. H. developed a vesicular eruption of the hands with a definite bimonthly cycle of exacerbations. She gave a 3-plus skin reaction to estrone and a recurrent flare in the test site. Desensitization was started on June 2, 1950, with .05 cc of 1 mg per cc concentration. This caused a flare and she was then given 0.2 cc of a 0.1 mg per cc concentration, subcutaneously. She received three injections per week until August 19, 1950. By this time she presented only increased redness and slight pruritus at the two estrone level peaks. To date she has continued at this status with no further treatment.

Mrs. J. B., a twenty-six-year-old white woman, was referred by a urologist (Dr. A. J. Leader) who was acquainted with the author's work. It was his feeling that certain cases of intractable urethritis presented a definite rhythmicity of flares which might well put them in the category of endocrine hypersensitive cases. This patient's difficulty usually occurred three to four days premenstrually and at mid-menses. Endocrine tests revealed a 3-plus reaction to estrone. During one of her bouts, Dr. Leader administered epinephrine aqueous which afforded her good relief. He then gave her epinephrine in oil with longer relief. Oral antihistaminic agents also gave relief. At present this patient is in California, where a physician is attempting desensitization under my direction. To us this seemed to suggest possibilities for endocrine hypersensitivity in many other syndromes presenting a definite periodicity.

COMMENT

Nineteen patients with history and clinical findings presenting definite rhythmicity were skin tested with endocrines. Table II contains an analysis of the acne cases.

From these observations and those of other workers a somewhat newer classification of acne vulgaris on an etiologic basis is evolved. The usual

case of adolescent acne is probably due to a combination of inadequate sebaceous gland ostia to which is added the factor of stimulation by the appearance in the blood of testosterone or in the female progesterone, which has testosterone-like activity. Other factors such as contributory foods or drugs and poor hygiene are also important. The male patients have a constant eruption. The females have recurrent flares synchronous with the elevation of progesterone level in the blood. This is another way of looking at change in ratio of the estrogen-androgen level previously mentioned, resulting in a relative androgenicity.

A second group occurs among females in whom there is an apparent constant eruption, but close observation and interrogation will reveal that there are bimonthly flares coincident with the increased level of estrone or estradiol. Many of these patients are definitely hypersensitive to such endocrines by skin tests. Cases B. D., S. C., and A. H. exemplify such cases. Estrogens in large doses did not help these cases. Their flares are bimonthly.

A third group appeared late in the series, two of whom revealed positive skin tests to progesterone. These patients also had monthly premenstrual exacerbations. However, whether their flares are based on a hypersensitivity to progesterone or whether there is merely a stimulating action has not been ascertained. The antagonistic action of estrones will help these cases. In those cases demonstrating marked reaction to skin tests, desensitization might be attempted.

In light of these results we must reappraise our methods of treatment. Endocrine skin tests are certainly not indicated in every case of acne. Only those cases with a very suggestive history and those who have been observed for some time should be tested. When the endocrine aspect seems to play a great part and the acne is not causing scarring, estrogens should be tried for a considerable period. X-ray is very helpful but should be restricted to the scarring type. It should also be used in males where moderate doses of estrogens do not help appreciably. One must always bear in mind the possibility of undesirable changes of secondary sex characteristics in males caused by female hormones. Local therapy and regulation of diet still have their place in treatment.

CONCLUSIONS

1. Hypersensitivity to endocrines in the guise of cutaneous disorders does exist, and desensitization is possible in a fairly large percentage of cases.

2. A rearrangement and selective re-evaluation of acne vulgaris on an etiologic basis, directed toward treatment methods, is presented.

3. Other organs and systems than the skin may present manifestations of hypersensitivity to endocrines. Awareness of such possibility should

(Continued on Page 781)

THE DIFFERENTIAL DIAGNOSIS OF COUGH IN TUBERCULOSIS AND BRONCHIAL ASTHMA

ETHAN ALLAN BROWN, M.D., F.A.C.A.
Boston, Massachusetts

AMONG the Italians there is a proverb to the effect that in the universe there are only three things that cannot be hidden or suppressed, namely, a cough, love, or a fire. The perspicacity of the anonymous author is shown in the fact that, in the triad, the cough is placed first. Of the fifty-odd signs and symptoms, the combinations and permutations of which help us distinguish between some 250 or more disease conditions, a cough is one of the most obvious. Varying in importance from the innocent psychogenic cough of the members of a bored and restive audience to the unbearably painful racking cough of the patient with tubercular laryngitis, it is a sign held in common by so many syndromes that it is sometimes one of the most puzzling of all signs to evaluate. A brief basic review will help us understand all the factors involved in its differential diagnosis.

There is nothing complex about the cough itself. The patient, after a short, quick inspiration, closes the glottis. Pressure on the inspired air is elevated by the muscles of expiration. This, the compressive phase of the cough, is immediately followed by the expulsive phase as the nasopharynx is closed and the glottis rapidly reopened so that the released air may forcefully expel any particulate matter in the upper respiratory tract. In those in whom the nasopharynx is not completely closed, the cough is followed by a second set of reflex actions, a sneeze. In others, it may initiate a third set of reflexes, namely, vomiting.

The neural impulses which cause coughing originate in the pharynx, larynx, trachea, bronchi, and the pleural surfaces. Generally sensitive is the mucous membrane of the bronchi, especially that of the first and second orders of division. The points of exquisite sensitivity are located in the mucosa of the trachea at the point of the bifurcation of the bronchi and on the surface of the larynx. A cough due to irritation of these surfaces cannot be suppressed.

The neural pathways, as is generally known, consist of the afferent fibres of the vagus, and the tractus solitarius. The cough center, responsible for voluntary coughing, lies in the medulla oblongata near the respiratory center. Reflex coughing travels by reflex arc to all the muscles concerned with inspiration and expiration. The control of the depth and strength of the cough is regulated by the abdominal muscles and the diaphragm.

In general, the causes of cough are mechanical and inflammatory. One thinks of inorganic, nonallergenic dust inhalation as mechanical, and of

---

Presented at the meeting of the American Academy of Tuberculosis Physicians, June 9, 1951, Atlantic City, New Jersey.

Dr. Brown is physician-in-chief, Allergy Clinic, Boston Dispensary Unit, New England Medical Center, Boston, Massachusetts.

smoking, chemical (often industrial) irritation, and of course, infections, as examples of inflammation. The allergist lists thermal causes in patients with physical allergy and sees asthmatic patients in whom cold air, as climatological, such as in going outdoors during the winter, or as extraseasonal, when exposed to extreme air conditioning during the summer, causes cough. In others, cold air may initiate cough because of the lowered temperature of the air, and in some cases, water both as inhaled and acting reflexly on the skin may bring on the gasping reflex and, therefore, a secondary cough. Such thermal changes act as precipitating agents often for a discoverable pathological lesion. In patients with physical allergy, no primary lesion is usually found.

We cannot discuss the most important coughs of tuberculosis and bronchial asthma unless we are clear in our understanding of some of the other types of cough which may be confused with both of these.

Faced with a patient who complains of cough, it is well to think in terms which, although not mutually exclusive, include all or almost all of the differential diagnoses to be considered. At the risk of seeming repetitious, these must be clearly differentiated. Considered in turn must be infection, reflex action, irritation, secretion, edema, ulceration, and pressure. Separately, or together, with additional key signs or symptoms, these will help distinguish between twenty or more different types of cough, some of which may be present concomitantly, as in a cigarette smoker who also wheezes, or in an asthmatic patient whose occupation is to repair oil burners or refrigerators. All the various types of cough cannot be listed or discussed, but only the most important pertinent or confusing as they appear in syndromes progressing down the upper and lower respiratory systems.

In acute pharyngitis, the history of infection or of mechanical or chemical irritation is easily elicited, and the local signs, varying from simple injection and marked inflammation, are obviously apparent. The high, dry, hacking cough is easily recognized. Pitfalls in diagnosis will be avoided if the possibility of diphtheria, fusospirochetosis, and streptococcal infections is considered. A once-in-a-lifetime diagnosis is a retropharyngeal abscess masking as an acute or chronic pharyngitis.

In chronic pharyngitis, there is the same high, dry, hacking cough, with a history of prolonged particulate physical, or nonparticulate chemical irritation. Infection, if present, is usually paranasal. Remembered, if only to be discarded, must be the possible diagnoses of lymphosarcoma and lymphoepithelioma, both of which I have seen. One day a boy of fourteen was brought in suffering from so-called sore throat and subacute pharyngitis, in whom the true diagnosis, made by inspection and corroborated by the laboratory, was infectious mononucleosis. Epidermoid carcinoma is sometimes given as causing a dry, hacking cough, mistaken for chronic pharyngitis. I have never seen a case of this kind.

In acute laryngitis, we have extension of the same process and with the same symptoms, but with one additional sign, voice change.

In chronic laryngitis, brought into the diagnostic picture are the possibilities of two additional chronic infections: first, the luetic cough associated with mucous patches, rare and becoming more rare; and second, the tuberculous cough.

The tuberculous laryngeal cough, due to local ulceration and caseation, is almost invariably early or soon associated with extreme pain. As is generally known, primary tuberculosis, usually pulmonary, is almost always also present. Errors in diagnosis occur in patients with papilloma of the vocal cords and in those in whom pressure upon the larynx or the pharynx by carcinomata, with or without ulceration or secondary infection, complicates the picture.

At this point, the pedunculated substernal thyroid should be considered. We have seen, in all, three clear-cut cases, in each of which there was no change in voice and the patient coughed when lying on one side and not on the other. The three diagnoses were, successively, "smoker's cough," "asthma due to fumes of range oil," and "chronic laryngitis," the cough being cleared in each patient by thyroid surgery.

At this point of the physician's thinking should be brought in the so-called diagnosis of "laryngeal vertigo," known also as "laryngeal epilepsy" or "laryngeal syncope," all due to Arnold's nerve reflex cough syndrome. In this rare condition may be seen all gradations of nonproductive coughing from the occasional sensation of tickling in the throat to the most severe coughing paroxysms, leading to and followed by syncope. In a patient with an extremely hypersensitive Arnold's nerve reflex, foreign bodies, such as loose scales or wax, or else infection of the external auditory canal causes such coughing. It appears that the condition is most frequent among obese, hypertensive, middle-aged males. One of our patients developed a cough of this type following a left-sided, acute otitis media. In these patients the cough can be reproduced by stimulation of the posterior, inferior portions of the external auditory canal and the posterior portion of the tympanic membrane. Treatment, as is well known, consists of the repeated applications of silver nitrate (50 per cent) to the areas which are controlled by Arnold's nerve.

In nonallergic or infective tracheitis, or in true tracheobronchitis, we must in the early stages rule out, especially in children, measles and whooping cough, and rarely in this country, typhoid fever. More often, infection will be due to the influenza virus, pneumococci, and streptococci. Inspection proves the presence of the red, swollen mucous membranes, the dry cough rapidly becoming productive.

In allergic, noninfective tracheitis, we have a sole cause for a single symptom. The hacking, dry, irritating, nonproductive cough in a patient who may have a history of what he terms "heavy breathing" and substernal

pressure, similar to that of angina, excepting that it is not as fearful and lasts for hours without incapacitating a patient, is known to every allergist. There is no history of infection conveyed to or from the patient. The substernal oppression is not associated with transmitted pain. The electrocardiogram is normal. The examination may show a pale, boggy, or sometimes an injected, irritated membrane. The physical examination of the chest demonstrates the typical sibilant and sonorous râles, changing in pitch and intensity as the stethoscope is held over any one region of the thorax. In pre-asthmatic allergic tracheitis, there may be no signs in the chest, or if they are present they may be subclinical, the patient being totally unaware of their presence, although the vital capacity may range from 20 to 50 per cent below normal. Allergic tracheitis may therefore occur as a pre-asthmatic state. The patient may never have had an attack of bronchospasm and may have no known history of bronchial asthma, although a history of other allergic syndromes may be present.

The cough is often intractable to codeine, Hycodan, or Mercodinone. It is worse at night, it is relieved in part or completely by ephedrine and antihistaminic agents, and it is completely cleared by elimination of the inhalant or food allergens or by specific injection treatment. An emotional factor almost always exists and may cause the return of the cough in times of distress or strain. The nonpassive expiration type of bronchial asthma is due, in part, to this type of coughing.

When the tracheobronchial tree is continuously assaulted by bacteria from above, especially from the teeth, tonsils, or sinuses, or else from below, as due to bronchiectasis, the chronic infection often associated with emphysema (or to mucus in asthma), a clinical syndrome, the existence of which most internists dislike to accept, is said to be present: namely, chronic bronchitis with or without wheezing. The signs of edema, hyperemia, and mucus secretion, worse following a cold in the early fall, with symptoms lasting all winter, and exacerbations with exposure to cold air, are some of the distinctive signs and symptoms. In asthmatic bronchitis, as in chronic bronchial asthma, the mucus may be grey and viscid and contain fibrin. It may be frothy and occasionally tinged with blood. Hemoptysis, although rare, does occur from laceration of pulmonary tissue or acute rupture of the alveoli. Pulmonary blebs and the results of acute localized pain, when occurring at the bases, may force a physician to think of pleurisy. In such patients, when they are allergic, the ability to cough productively usually signals the beginning of the end of the asthmatic attack. If such patients wheeze, and allergic causes are ruled out—and infectious causes are seen as the predominant factor—they are said to suffer from asthmatic bronchitis. Their sputum lacks the typical Curschmann's spirals, the Charcot-Leyden crystals, and the eosinophil cells seen in a typically allergic patient with bronchial asthma.

If treatment is to be directed against a cough in these two types of asthmatic patients, its timing in the asthmatic attack must be given careful

thought. The patient who goes into bronchospasm, with no antecedent cough, is often easily relieved by antispasmodic agents which signal their effect by initiating cough. The patient suffers from an allergen-caused edema of the bronchial mucosa and reflex spasm of the bronchial musculature. He responds to his now relaxed bronchioles by bringing up the newly released, inspissated mucus. To treat this type of cough with codeine, or similarly acting medications, prolongs the attack, out of which the patient wishes to and must cough his way.

On the other hand, the patient with chronic bronchitis, so-called, coughs his way into an attack of asthma. He needs antitussive medication sufficient to prevent his bronchospasm and yet not so much so that useful expectoration is suppressed. Such medicines as codeine can be prescribed. The fact that we are trying to follow such apparently contradictory courses in treatment forces us to add expectorants to our cough-depressant prescriptions, something we never do when prescribing antitussive medication for tuberculous patients, in whom such expectorants cause both a relative and often absolute increase in the number of acid-fast bacilli.

It might be well at this point to discuss emphysema, which is not, as is generally supposed, due to forceful expiration. It is not seen in players of wind instruments, unless they become secondarily emphysematous or bronchitic. It is due to the action of the inspiratory effort upon blocked pulmonary tissue. The lung is supported by the thoracic wall during expiration but not during inspiration. The suction traction of the more powerful muscles of inspiration are therefore concerned. This is the explanation for the appearance of the bullae at the areas of least support, the apices, the sternal and the diaphragmatic margins of the lungs. These are the patients who do well in Arizona, Colorado, Southern California, Texas, and Florida. They are the patients for whom, as George Bernard Shaw put it, "the honest physician should be able to prescribe, not medicine, but money."

The typical severe coughs of the congestive, irritative, inflammatory, and obstructive types of bronchiolitis, with equally typical, copious, purulent mucus, often in advanced cases containing granulation tissue and blood, are rarely mistaken as allergic or tubercular in origin. When the obstruction is due to foreign bodies, it should be remembered that in only one patient in seven is there a history of having inhaled such foreign bodies, and that in only one patient in thirty is it ever coughed up.

In bronchogenic carcinoma, if the discussion is limited to the patient who coughs, the cough will depend upon the type of growth. The remaining symptoms will depend upon the location of the neoplasm. The associated blood, the dyspnea, the localized wheeze, and the collapse, often with fever, are physical signs out of all proportion to the size of the lesion. In this regard, Osler's aphorism that "Half the diagnosis of bronchogenic carcinoma consists of looking for it" should be considered during every physical examination of the chest.

To complete the list, and not likely to cause diagnostic difficulty are pulmonary abscess and gangrene, and the fungous and parasitic infections, as well as the pneumonias. In tropical eosinophilia there is the blood picture, the x-ray findings, and the response to arsenicals. Pneumoconioses are industrial problems, not often seen in general practice. Typical active pulmonary congestion and the early stages of infectious and passive pulmonary congestion and edema will not be puzzling because of the usually obvious cardiac or other lesions present.*

The cough of empyema, as associated with its usual pus and the ringing brass of an aneurysm, are equally distinctive. Infarction by embolus or thrombus does not usually cause errors in differential diagnosis.

The cough due to atomic bombing is similar to that seen in "blast lungs" of air raids and is due to compression of the chest rather than to lung injury. The cough is due to the hemorrhagic exudate in the interstitial lung tissue and the alveolar spaces. In such cases, the cough, which starts in forty-eight hours, is associated with dyspnea and cyanosis, expectoration, and hemoptysis. The x-ray film is typical. A transfusion or intravenous fluid will cause the recurrence of the pulmonary bleeding. Secondary bronchopneumonia is the usual sequel.

The different types of cough seen in pulmonary tuberculosis require detailed discussion. At the medical school, we teach our students that cough is usually the first and last symptom of pulmonary tuberculosis, although we all know that this is not quite true. Although it is a frequent, almost constant, sign, there are rare tuberculous patients who do not cough. In some of these, especially women, the mucus is raised by ciliary action and swallowed with minimal or no coughing. In some tuberculous patients the cough may be soft and infrequent, and in one patient I saw, a barber with bilateral involvement, the differential diagnosis was suggested by the fact that the cough followed each meal and progressed into emesis. He was said to be food sensitive.

The emetic cough is a traditional sign of tuberculosis. It may occur with the first mouthfuls taken, or during the meal, or immediately afterwards. There is neither nausea nor gastric distress, the vomiting coming on suddenly and during a coughing spell. The patient frequently wishes to eat again, and only learns in time that the cough and vomiting are due to the food ingestion itself, and especially to hot drinks or heavy meals. The term "Morton's cough" cannot be given to those tuberculous patients who have chronic gastritis or suffer from alcoholism, and it is not to be applied to the vomiting of late tuberculosis when there is no preceding cough. The true "Morton's cough" occurs early in the disease in patients with no gastric dysfunction, and as noted, in those in whom there is no nausea or retching. It often occurs at a specific time after eating, the sequel of events

*Pressure upon the bronchi and change in their angulation is the explanation for the cough accompanied by the enlarged left auricle of mitral stenosis and the enlarged left ventricle of hypertensive or coronary heart disease.

being the tickle in the throat, a cough, and sudden gastric evacuation, leaving the patient feeling well and often anxious for more food.

Similar coughs are seen in pertussis and, occasionally, in pharyngitis. They may occur in chronic alcoholics, but the sign is typical of no other syndrome except tuberculosis. It is never seen in bronchial asthma, except in children in whom coughing may cause vomiting, in this case not related to meals. We give asthmatic children ipecac to initiate pulmonary mucus evacuation. Such coughs are therefore not to be mistaken for a true "Morton's cough."

The Morton type of cough is due to the massage of the bronchial tract by the passage of food down the esophagus. The sputum is loosened, especially following the ingestion of hot foods. The resulting irritation causes the cough and vomiting. It differs from the emesis which occurs from the aspiration of food in the toxic tuberculous patient, with fatigue of the glottis. This cough differs entirely from the cough in the adult asthmatic patient, in whom the taking of cold food, such as ice cream, causes a reflex spasm of the bronchial tree and an attack of bronchial asthma. Such spasm in asthmatic patients is relieved by hot food, as it is occasionally by heat applied to the anterior thoracic wall. Ephedrine by mouth often relieves both the asthmatic and the tuberculous types of cough, and cannot be used to differentiate between them.

In acute tuberculosis, which we all recognize as almost always, if not always, an acute exacerbation of a chronic, usually unrecognized, tuberculous infection, there may be a history similar to that of early extrinsic bronchial asthma. There may be a history of fatigue, night sweats, cough, and expectoration for weeks, usually for months, in both conditions. The cough in acute tuberculosis may resemble that of a pneumonia, first dry and then productive, with either frothy, mucopurulent or viscid and rusty mucus, rarely bloody. The patient may then appear to have a true pneumonia. The pulse, however, instead of being strong and forceful, is rapid and weak. The response to antibiotics is, of course, limited.

In other tuberculous patients, the onset may be similar to that of intrinsic bronchial asthma. The patient has had a history of winter grippe or chronic colds. The cough in such tuberculous patients may occur in the morning, or perhaps only at bedtime. Some of these may resemble the extrinsically asthmatic individual, in that the cough persists until a small, hard lump of mucus is expelled, following which the cough subsides.

In tuberculous patients referred because of the associated wheeze, the breath sounds are not harsh and tubular, but often dim or absent, with moist subcrepitant râles. In three cases I have seen, the asthenia, anorexia, and rapid emaciation were immediately marked in two. These patients were mistakenly considered as weak, due to the lack of sleep. In two, the hyperpyrexia was minimal. In the third, it rose and continued high. In this patient, an Episcopal clergyman, death occurred in four weeks.

In the severe tuberculous patient, the cough is, of course, paroxysmal and

may extend from the ordinary, moderate coughing, controlled by codeine, to such severe paroxysms that the patient may "black out." Such severe coughing also occurs occasionally in the asthmatic patient. In both, the Arnold reflex cough may be considered, but will rarely, if ever, be diagnosed.

To complete the list, my pediatric colleagues tell me that there is a peculiar cough, or stridor, common to both asthmatic and tuberculous children, the symptoms being continuous and lasting for months. I have been fortunate in never having seen a tuberculous child with this type of "hoarse puppy" cough. To my knowledge, we have never made a diagnosis of tuberculosis in the many children we see, probably because they have all been screened out before reaching the clinic, although we think of tuberculosis in every child in whom no other clear-cut diagnosis can be made.

To repeat, if only for emphasis, the cough seen in the typically allergic patient frequently occurs in the morning on arising and at bedtime, when it is not due to exposure to an allergen. It may show itself as an allergic tracheitis, or in the chronically asthmatic patient, it may present itself as the cough of chronic bronchitis. It differs completely from the cough of the tuberculous patient who is emptying a cavity and from the bronchiectatic cough, in that it does not occur with change in position. It differs also from the cough seen with body twisting or turning as occurs in pleurisy, which is, however, distinguished from the other types of cough by being nonproductive.

It is noted that in both asthmatic and tuberculous patients, hemoptysis may occur with prolonged or severe coughing and the presence of blood is therefore not of diagnostic value in ruling out bronchial asthma or tuberculosis. In general, the tuberculous patient responds better to codeine and its substitutes and is worse with expectorants, especially the iodides, which exert lytic effects. The asthmatic patient responds poorly to codeine and well to iodides, an ingredient in almost every drug mixture used in the treatment of bronchial asthma.

In both conditions, also, there is one additional confusing factor. It was once taught that in any cough lasting more than a month, tuberculosis should be suspected. We have, however, patients with bronchial asthma who have coughed for years with no physical signs or radiological proof of tuberculosis. The hysterical or neurogenic cough, as is generally known, may also go on for a long period of time and cause no ill effects.

True confusion may occur in the patients who have both bronchial asthma and tuberculosis. In some asthmatic patients, in whom the x-ray findings are those of healed or arrested tuberculosis, we can sometimes elicit a history of a tuberculous infection as deduced from a so-called attack of influenza, grippe, or bronchitis, which lasted four to six weeks and was marked with cough, weakness in the late afternoon, and tachycardia. If the temperature was taken, there was a typical afternoon elevation and an early morning depression. These patients with healed tuberculous lesions

are rarely diagnosed as incipient or early tuberculosis, unless hemoptysis occurs. When the diagnosis is made and sanatorium treatment is instituted, recovery is usually rapid and complete. The allergist who is a consultant in a tuberculosis sanatorium sees many tuberculous patients who present wheezes, and few, if any, asthmatic patients who develop tuberculosis. Some of the first group may suffer a bronchitis deformans and both an inspiratory and expiratory wheeze, but usually the two conditions are quite separate, the patient having first suffered a tuberculosis, now healed, and a second condition, namely, bronchial asthma, or a tuberculosis associated with bronchial asthma. If the asthma becomes sufficiently severe in the healed patient, the acid-fast infection may be reactivated and the patient then suffers from both conditions together.

In 1950, in a discussion of tuberculosis and asthma, I stated that I had not seen an allergic asthmatic patient acquire tuberculosis. I have since had one of my hay fever asthmatic patients admitted to the Essex County Sanatorium for a minimal lesion, which healed within a year. There were no antecedent symptoms, the previous roentgenograms having been negative, the lesion being discovered on a routine pre-college entrance x-ray film.

In summary, in the differential diagnosis of cough, we must separate the relevant from the irrelevant factors. The causes of the common coughs are easily recognized. In patients whose cough is atypical, the chest surgeon thinks of bronchogenic carcinoma, the allergist thinks of allergenic causes, and the tuberculologist, of acid-fast infection.

The cough of neoplastic development, when it is a symptom, may be early or late. Its possibility should be considered in any patient presenting a cough not due to an easily recognized, clearly diagnosed acute condition.

The allergic cough manifests itself as allergic tracheitis or as a preasthmatic sign. It may initiate spasm in the nonpassive type of expiration asthma, often associated with infection, or signal the end of an attack of true bronchial spasm when it serves to bring up previously trapped mucus. An allergic cause should be entertained if tuberculosis or neoplastic causes are eliminated.

The tuberculous cough will differ as to the site of the lesion. In acute tuberculosis, it may at first resemble the cough of acute bronchitis and pneumonia. It may simulate the cough of any other condition affecting the upper and lower respiratory tracts, being perhaps pathognomonic only, it being associated with a local pain in the acid-fast infection of the upper respiratory tract. Its presence should be suspected in any chronic cough of any type.

If the unusual causes of cough are kept in mind, few patients presenting cough as their chief symptom will go very long without accurate diagnosis and specific treatment.

75 Bay State Road

A NEW SYMPATHOMIMETIC AMINE ("NEOSUPREL") IN THE TREATMENT OF BRONCHIAL ASTHMA

J. AARON HERSCHFUS, M.D.; ELLIOTT BRESNICK, M.D.; LEON LEVINSON, M.D., and MAURICE S. SEGAL, M.D., F.A.C.A.

Boston, Massachusetts

EFFICIENT management of patients with bronchial asthma is based largely upon the use of sympathomimetic amine aerosols for rapid relief of bronchospasm with minimal side reactions. Compounds suitable in this connection must be good sympathin I-mimetic agents with little or no sympathin E-mimetic properties, so that they will produce bronchodilatation without adverse effect upon the heart and circulation.

We have previously reported the properties of isopropylarterenol (Isuprel®), a substance in which substitution of an isopropyl radical for the methyl group of epinephrine yields enhanced bronchodilator activity.[3,5] It is impractical to employ Isuprel as an aerosol in concentrations greater than 0.5 per cent, however, due to the occurrence of palpitation, tachycardia, tremor, and other evidences of sympathin E-mimetic activity. Ethylnorepinephrine, on the other hand, is a less potent bronchodilator than epinephrine, but it causes fewer and less marked subjective side effects than epinephrine.[1,2]

Of a variety of derivatives of ethylnorepinephrine and isopropylarterenol (Isuprel), the most promising is 1-(3,4-dihydroxphenyl)-2-isopropylamino-1-butanol hydrochloride ("Neosuprel")* in which the isopropyl grouping of isopropylarterenol is substituted on the nitrogen of the ethylnorepinephrine nucleus (Fig. 1). In animal experiments Neosuprel exhibits somewhat less activity as a bronchodilator than does Isuprel, but it has only 1/16 to 1/80 the cardiovascular stimulation properties of Isuprel.[6,7] In the belief that this substance would be a very desirable bronchodilator drug, we have subjected it to laboratory and clinical investigation.

METHOD

The bronchodilator activity of various therapeutic agents may be measured in man by estimation of the degree of protection they confer against the change in vital capacity which may be induced at will in sensitive asthmatic individuals by the administration of histamine or methacholine. The technique of these studies has been described in detail, and results with

From the Department of Inhalational Therapy, Boston City Hospital and the Department of Medicine, Tufts College Medical School.

This study was aided by a grant from Winthrop-Stearns, Inc.

Doctor Herschfus is Research Fellow in Medicine, Tufts College Medical School.
Doctor Bresnick is Assistant in Medicine, Tufts College Medical School.
Doctor Levinson is Assistant in Medicine, Tufts College Medical School.
Doctor Segal is Director, Department of Inhalational Therapy, Boston City Hospital; Clinical Professor of Medicine, Tufts College Medical School.

Approved for publication, August 2, 1951.

*Kindly supplied by Winthrop-Stearns, Inc.

many agents in common use for the management of bronchial asthma have been presented.[3] In brief, the method consists of the repeated administration of a bronchospastic drug at half-hourly intervals, before and after the

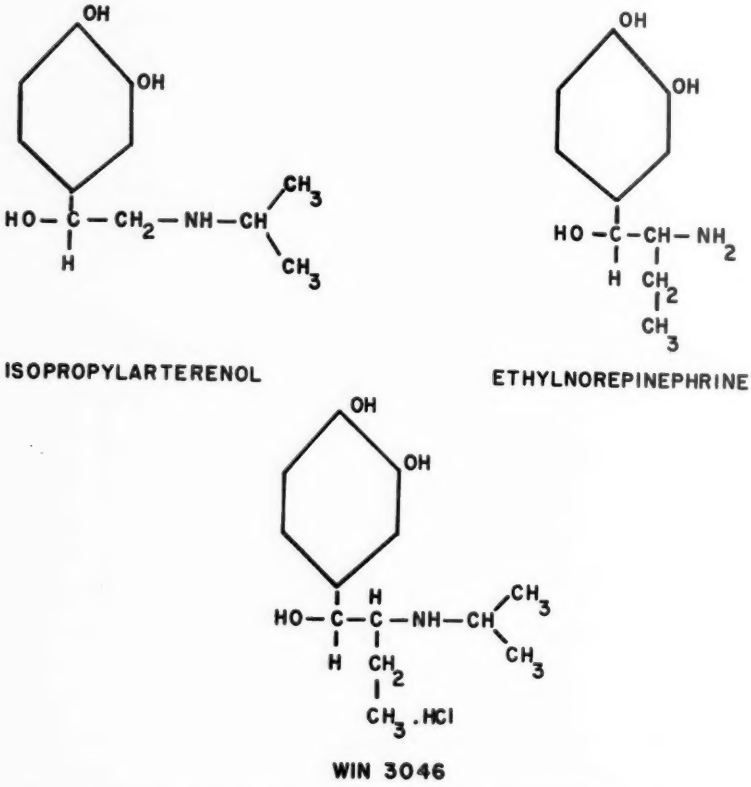

Fig. 1. Structural formulae of Isopropylarterenol, Ethylnorepinephrine, and Neosuprel.

administration of the protecting agent to be tested, and the measurement of the protection conferred is expressed in terms of the following equation:

$$P = \frac{C - E}{C} \times 100,$$

where P = degree of protection in per cent, C = control decrease in vital capacity produced prior to administration of the therapeutic agents, and E = decrease similarly induced after the protecting drug has been given. Because of the limitations of any technique of bioassay in humans, protection values below 40 per cent are considered insignificant, and all values are computed as averages of experiments on at least five asthmatic individuals.

TABLE I. BRONCHOSPASTIC AGENT

Bronchodilator Drug	Histamine I.V.		Methacholine I.V.	
	Immediate Protection (%)	Duration of Significant (More than 40%) Protection (Min.)	Immediate Protection (%)	Duration of Significant (More than 40%) Protection (Min.)
Epinephrine 1.0%	75	28	56	18
Isuprel 0.5%	70	22	69	42
Isuprel 1.0%	98	62	91	81
Neosuprel 1.75%	73	45	82	45
Neosuprel 2.5%	80	45	86	64

RESULTS

Protection Studies.—The results obtained when various sympathomimetic amine aerosols are tested in this way are presented in Table I. Neosuprel was tested in a 2.5 per cent and 1.75 per cent dilution.

It may be seen that Neosuprel, 2.5 per cent, is almost as effective in protection against histamine- and methacholine-induced bronchospasm as is Isuprel, 1.0 per cent, and more effective than the 0.5 per cent (1:200) solution. A 1.75 per cent solution of Neosuprel is about as effective as the 2.5 per cent solution. In general, these studies indicate that Neosuprel is similar to Isuprel in bronchodilator action, and about one half as potent by weight as the latter agent.

Clinical Trials.—Neosuprel, 2.5 per cent, was supplied to twenty-six patients with severe chronic bronchial asthma, who had previously been employing aerosols of Isuprel, 0.5 per cent. Eighteen patients preferred Neosuprel, 2.5 per cent, to Isuprel, 0.5 per cent. More prolonged bronchodilator activity was commonly reported. Seven patients preferred Isuprel to Neosuprel, in most cases because of the disagreeable taste of the latter preparation. One patient was unable to differentiate between the two substances.

Ventilatory Studies.—

(a) 2.5 per cent Neosuprel Solution.—The bronchodilator potency of Neosuprel is appreciable even when the patient himself is not aware of bronchospasm. In 102 such individuals, 1 cc of the 2.5 per cent solution was given aerosolized with oxygen. It produced a rise in vital capacity ranging from 100 to 1600 cc, averaging approximately 342 cc. This compares favorably with our previous data on Isuprel, 0.5 per cent.[4] In another group of thirty patients with asymptomatic or mild bronchial asthma, there was a 17 per cent improvement in vital capacity after six inhalations of the 2.5 per cent solution. The average vital capacity rose from 3.49 liters (range 1.4 to 5.6 liters) to 3.94 liters (range 2.0 to 6.0 liters).

This latter group of patients experienced an average of 50 per cent improvement in the maximum breathing capacity (MBC). The average MBC (35 determinations) before treatment was 63 per cent of predicted normal value and rose to 85 per cent of predicted normal after the use of six inhalations of the 2.5 per cent Neosuprel aerosol. If we divide the pretreatment MBC's into four groups,—(1) less than 25 per cent of the predicted value; (2) between 26 per cent and 50 per cent of predicted value; (3) between 51 per cent and 75 per cent of predicted value and (4) 76 per cent of predicted value or higher,—then the average values of improvement are 103.7 per cent, 83.6 per cent, 44.1 per cent and 15.6 per cent respectively. (Table II).

TABLE II.
MAXIMUM BREATHING CAPACITY

Number of Tests	% of Predicted Normal Values Before Treatment	Improvement (%) After 6 Inhalations of Neosuprel, 2.5%
2	Less than 25	103.7
9	26–50	83.6
11	51–75	44.1
13	More than 75	15.6
35		

(b) 1.75 per cent Neosuprel Solution.—The 1.75 per cent solution, six inhalations, was given to thirteen asthmatic subjects. The average vital capacity before treatment was 1.98 liters (range 1.1 to 3.6 liters) and rose to 3.13 liters (range 1.9 to 5.5 liters). To another group of forty-nine patients, 1 cc of the 1.75 per cent solution was given aerosolized with oxygen. The vital capacity in this group rose from an average of 2.80 liters (range 1.4 to 4.8 liters) to an average of 3.35 liters (range 2.2 to 5.4 liters), an average improvement of 550 cc.

The maximum breathing capacity was tested in five patients before and after six inhalations of the 1.75 per cent solution; there was a 45 per cent average improvement.

REACTIONS

In none of the patients did tachycardia, palpitation, tremor, or other side effects appear following the administration of six inhalations of this aerosol (2.5 per cent and 1.75 per cent). In fact, six patients with hypertension as well as bronchial asthma in whom Isuprel regularly induces palpitation, did not experience this reaction with Neosuprel. However, 1 cc of this solution aerosolized frequently will result in cardiovascular stimulation.

The cardiovascular response to Neosuprel, 2.5 per cent, aerosol has been studied in detail in five individuals who entered the laboratory in acute paroxysms of bronchial asthma. A total of thirteen administrations of six inhalations was studied. The average maximum alteration in blood pressure was a fall of 2 mm in systolic pressure and 6 mm in diastolic pressure, with no change in pulse rate. In no patient was any significant rise in blood

pressure observed. The maximum drop observed was 27 mm systolic, associated with an 8 mm drop in diastolic pressure and, in another individual, a 35 mm drop in diastolic pressure, accompanied by a fall of 12 mm in systolic pressure. None of these cardiovascular responses were subjectively manifest.

Neosuprel in the form of sublingual tablets, 10 mg, was given to five patients. None reported beneficial effect, all preferred the preparation by aerosol, and three patients experienced unpleasant reactions such as tremor, palpitation, or tachycardia.

CONCLUSIONS AND SUMMARY

We have tested in the laboratory and clinic a new sympathomimetic amine, 1-(3,4-dihydroxyphenyl)-2-isopropylamino-1-butanol hydrochloride (Neosuprel), which combines the chemical groupings of isopropylarterenol and ethylnorepinephrine.

An aerosol produced from a 2.5 per cent solution of this compound protects sensitive asthmatic individuals against the bronchospastic effects of histamine and methacholine in a manner and degree comparable to an aerosol made from a 1 per cent solution of Isuprel. Whereas 1 per cent Isuprel aerosol produces marked systemic side effects, these are comparatively infrequent with Neosuprel in concentrations as high as 2.5 per cent.

Approximately three fourths of the asthmatic patients studied preferred 2.5 per cent or 1.75 per cent of Neosuprel to 0.5 per cent of Isuprel for use as a bronchodilator spray. Most of the patients were unable to differentiate between the 1.75 per cent and 2.5 per cent solutions.

REFERENCES

1. Cameron, W. M., and Tainter, M. L.: Comparative actions of sympathomimetic compounds: bronchodilator actions in bronchial spasm induced by histamine. J. Pharmacol. & Exper. Therap., 57:152, 1936.
2. Pedden, J. R.; Tainter, M. L.; and Cameron, W. M.: Comparative actions of sympathomimetic compounds: bronchodilator actions in experimental bronchial spasm of parasympathetic origin. J. Pharmacol. & Exper. Therap., 55:242, 1935.
3. Segal, M. S.: The Management of the Patient with Severe Bronchial Asthma. Springfield, Ill.: Charles C Thomas, 1950.
4. Segal, M. S., and Beakey, J. F.: Management of bronchial asthma. The use of 1-(3, 4-dihydroxyphenyl)-2-isopropylaminoethanol. Ann. Allergy, 5:317, 1947.
5. Segal, M. S., and Beakey, J. F.: The use of Isuprel for the management of bronchial asthma. Bull. New England M. Center, 9:62, 1947.
6. Sigmund, O. H.; Granger, H. R.; and Lands, A. M.: The bronchodilator action of compounds structurally related to epinephrine. J. Pharmacol. & Exper. Therap., 90:254, 1947.
7. Tainter, M. L.; Pedden, J. R.; and James, M.: Comparative actions of sympathomimetic compounds: bronchodilator actions in perfused guinea pig lungs. J. Pharmacol & Exper. Therap., 51:371, 1934.

370 Commonwealth Avenue
(Doctor Segal)

PERIORBITAL DERMATITIS

BOEN SWINNY, M.D., F.A.C.A.
San Antonio, Texas

DERMATITIS about the eyes has been the most frequent of the regional dermatoses recently observed in my private practice of allergy. Ten or fifteen years ago, a review of my cases would have shown that 90 per cent were due to nail dye and liquid nail polishes. In fact, this was so universally observed that many of us were speaking of dermatitis of the lids as "nail dye dermatitis." Since the war, in my experience, the etiological picture has changed. The knowledge that nail cosmetics are so frequently the cause has become the property of the general profession, beauticians, and the more intelligent and informed laity. All except three of this series of patients had left off nail dye without recovery before presenting themselves at my office for investigation. This study of possible causes was begun three years ago in order to try to gain some knowledge of how to approach the study of our cases in order to achieve cure quickly and efficiently. The results of my experience are presented in the form of overall conclusions instead of individual case histories, as a series of sixty-three consecutive cases would be prolonged and boring.

PATHOGENESIS

The eye and adjacent area is one of the most vulnerable regions of the body. Small foreign bodies and secretions accumulate at the inner canthus. These are removed at least a few times every day by everybody, by finger, tissue, or handkerchief. By this means many things are deposited. Because of the thin and relatively more permeable skin with its loose subcutaneous tissue, edema may result either from irritation or from sensitization by these substances. Whether the edema and subsequent train of events is due to sensitization or irritation is interesting scientifically but of little practical importance clinically. Because of the fact that the edema is often present on awakening, to disappear during the day, several of the patients I have seen have had renal studies. Itching is often present and when present, in my opinion, is a strong indication of a sensitization mechanism. Certainly, when present, rubbing with finger or handkerchief becomes very frequent and traumatizing, transmitting more foreign substance to the area, and serous exudation with perhaps some secondary superficial infection occurs. Usually, after a few days the edema and oozing subside, and the dry, cracking, perhaps exfoliative stage begins. Itching and discomfort increase. It is at this stage that the patient demands or uses some ointment, and then the cycle of edema and exudation starts over

Presented at the Seventh Annual Congress of The American College of Allergists, February 11-14, 1951, Chicago, Illinois.
Approved for publication July 20, 1951.

again. This cycle is a very noticeable feature, especially in long-continued cases, and is strongly indicative of the factor of overtreatment.

DIFFERENTIAL DIAGNOSIS

There is no relationship between conjunctivitis and periorbital dermatitis except that drops or ointments used for the former may sensitize and produce the latter (this occurred in six of this series of cases). Seborrheic dermatitis is readily differentiated by the other areas which it characteristically involves. Other differentials are easy.

I now present the results of my study of sixty-three recent consecutive cases of periorbital dermatitis. These results are not expected to be applicable to all periorbital dermatitis occurring in all parts of the world seen by those who use various modalities of practice. My approach has been purely clinical, relying on history, contact and intradermal testing, and avoidance and reapplication of suspected agents. Sixty-one of the patients were cured by removing the cause. In two patients no positive cause could be found, and these continue to have their dermatitis. These I labelled, as a last resort, "neurodermatitis." Although the factor of neurodermatitis was strong in many of the chronic cases, they got well when the real causative factors were found. The term "neurodermatitis" is often misapplied to patients who have not been sufficiently investigated for the precipitating or primary cause of their skin disease.

History, as in the study of all disease, is the most important part of the examination. As will be seen from the brief conclusions, emphasis should be placed on the listing of the cosmetics used, especially about the head, and topical treatment used. History of background of allergy, personal or family, is interesting but has proved to be of no significance *per se*. Occupational and hobby history helped in only three of the sixty-three patients.

Contact testing has been the second most important step toward diagnosis. Based on the history of cosmetics and topical applications used by the patient, tests have been applied in dilutions known not to react on normal skins. In general, it has been found that soaps and shampoos have to be used no stronger than 3 per cent under covered patches; otherwise positive reactions of no clinical significance are obtained. Tests are applied where the patient can see the reactions in order to overcome skepticism, especially in the chronic female, fat and forty, with too much make-up. All of the sixty-three patients gave positive reactions, many of these proving to be of no causative significance. Multiple reactions were the rule, but the reacting substances usually were related; for example, a patient sensitive to mercury usually had reactions to other metals, or the patient sensitive to Lustre Creme shampoo reacted also to other cream-based shampoos.

Trial and error, avoidance with clearing of the skin, with reapplication of each suspected agent serially at weekly intervals, has proved of course the best and most infallible answer. But I have found that unless the patient can be convinced by seeing positive reactions, I can get very poor

co-operation from advising against the use of all topically applied substances. That is the reason I do testing on all patients even though the history might be adequate to me. Also, I have found it difficult to persuade patients to experiment with reapplication after they are cleared. I succeeded in having twelve of the shampoo cases (forty-four cases) try their shampoo or a related shampoo again and they had recurrences. Three other patients came back to the office with recurrences and were found to be using their reactive cosmetics again.

All this series of patients had a study for atopic disease and intradermal skin tests for our most frequent inhalant and food allergens. Ten of the sixty-three patients had atopic disease, but there was no correlation with the dermatitis except in three who had the dermatitis as a result of sensitivity to Antistine eyedrops used for conjunctivitis.

Of the sixty-three patients studied, 85 per cent were female, 15 per cent male. There was only one nineteen years of age or younger, three over seventy, three of sixty to sixty-nine years of age. Thus, 88 per cent were between twenty and sixty, 85 per cent female, a strong indication that cosmetics play the major role.

Cream-based shampoos proved to be the most frequent cause in this series, with forty-eight positive reactions, forty-five of which proved to be of clinical significance. When found to be reactive to one brand, they were usually reactive to other brands. Lustre Creme, Halo, and Vita Fluff were most frequent. This does not indict these brands or this type of shampoo; they happen to be the most widely advertised and used shampoos in my community, and cream-based shampoos are now almost universally used in my community. Only four of these patients reacted to highly purified nonperfumed lanolin. I do not know why these shampoos produce dermatitis. Liquid powder foundations were causative agents in seven cases, six of which fell into the above group of shampoo cases.

Soaps have been hard to evaluate. Forty-nine cases reacted to 3 per cent dilutions of various soaps, but as a general rule the use of soap subsequently did not produce recurrences except in nine cases where colored or perfumed soaps were at fault. In general, I concluded that the usual brands of white soap were clinically harmless in periorbital dermatitis.

Overtreatment was responsible for periorbital dermatitis, wholly or in part, in twenty of the cases: yellow oxide of mercury ointment, six cases; antihistaminic ointment and eye drops, five cases; sulfathiazole ointment, two cases; Surfacaine ointment, two cases; analgesic and anesthetic ointments, four cases; miscellaneous (ointments—penicillin, Cuticura, et cetera), three cases.

Nail dye and polish was the cause in only three of my cases. These were the three women who had not been advised to remove it before coming to me. In ten other cases who had removed it without cure there were positive reactions, and the nail dye proved to be a partial cause along with another cosmetic or topical application.

An occasional instance of significant reactions was found to hair dye, rouges, powders, deodorants, eyelash preparations, and cologne, but the incidence of these and the incidence of reactions to the modern cold wave fluids were much less than expected. I must mention in passing two patients who were reactive to the red plastic frames of their glasses (negative to clear plastic), who would not clear up until they had discarded their red frames, and another woman who would not clear unless she left off her lipstick ten days (negative contact test). The reapplication of lipstick resulted in recurrence of her periorbital dermatitis within three or four days on two subsequent occasions (lips not involved).

Occupational and plant sensitivities occurred in only three patients: a nut merchant sensitive to the oil of pecan, a file clerk sensitive to carbon paper, and a rancher sensitive to weed contactants. In my office I see a great deal of weed and plant dermatitis, but periorbital dermatitis has been of plant origin in only one instance.

Multiple sensitivity has been the rule. Fifty per cent of the cases had had their dermatitis longer than three months when they consulted me, the longest involvement being thirty-eight years. The longer the duration the greater the number of causative agents found.

I avoided active treatment in order not to mar the study of cause. Topical treatment was limited to ice water compresses for the edematous-exudative stage and highly purified cottonseed shortening or hog lard for the dry, exfoliative stage.

CONCLUSIONS

Cosmetics are by far the most frequent cause of periorbital dermatitis, with the cream-based shampoos (together with the powder foundations) running a close second to nail dyes and liquid polishes. Overtreatment is third, with occupational causes running a poor fourth. Atopy plays little or no direct part and need not, in general, be considered in the study of this condition.

314-20 Medical Arts Building

DISCUSSION

STEPHAN EPSTEIN, M.D., Marshfield, Wisconsin: Doctor Swinny's report is interesting. There are several points which may be discussed. One is the change of allergens responsible for a dermatitis in a certain location. As Doctor Swinny said, ten years ago 90 per cent of these cases would have been diagnosed as nail polish dermatitis; in the present series about 75 per cent reacted to cream base shampoos and only about 20 per cent to nail polish. Another point of interest: Doctor Swinny's list of offenders is relatively small compared to that compiled some year ago by Hazen.

I have to congratulate Doctor Swinny on being able to find the cause of sixty-one out of sixty-three consecutive cases of dermatitis of the eyelids. In my material there are many more unsolved cases. I believe that atopic dermatitis of the eyelids is not quite as rare as one would gather from Doctor Swinny's statistics, although I admit that atopic dermatitis restricted to the eyelids without other locations, for

instance on the neck, is a relatively infrequent condition. However, I firmly believe that the diagnosis of atopic dermatitis of the eyelids is not made just by exclusion, after all contacts have been ruled out—or nearly so. Atopic dermatitis of the eyelids is usually a chronic dermatitis; the patches sometimes resemble the infiltrated lesions of nail polish dermatitis; usually they are less sharply outlined. Another diagnostic help is the fact that atopic dermatitis of the eyelids is not as symmetrical as contact dermatitis. Usually it is either confined to one eye or more severe on one side.

I have found that these cases of atopic eyelid dermatitis respond very nicely to desensitization with a dust-mold-bacterial mixture. Naturally, in all these cases one has to exclude the possibility of additional contact factors. Not infrequently there is a combination of an original atopic dermatitis with a secondary contact dermatitis, either from medication or cosmetics.

I agree with Doctor Swinny that skin tests should be performed, even if the history indicates the causative factor fairly well. At times even a very suggestive history gives a wrong clue. Moreover, a positive patch test will help to convince a patient of the necessity to eliminate that particular allergen.

Again, I would like to congratulate Doctor Swinny on having brought to our attention the great role of cream base shampoos in dermatitis of the eyelids.

GEORGE L. WALDBOTT, M.D., Detroit, Michigan: Relatively little attention has been paid by dermatologists and allergists alike to the pattern of dermatitis as a means of making a causative diagnosis. If we look closely at a lesion about the eyes, we may be able to arrive at a definite conclusion concerning its causes before a history is taken or patch tests are performed. For instance, if the corners of the eyes are involved, and if the lesions extend downward in a vertical streak, we suspect eye drops which run down from the corners. Sensitivity to an ointment that has been applied gives rise to a homogeneous lesion which is evenly distributed on both lids and usually sharply delineated. If the skin of the upper lid, especially its medial portion, is the site of irritation, the condition is usually due to rubbing this area with fingers contaminated by nail polish, face cream, hair lotions, or other semifluid materials. Dermatitis from mascara is localized in an area near the eyebrows. I saw a dermatitis from a hair net which was localized about the eyebrows and the upper eyelid, affecting the cornea and causing complete blindness. Detection and elimination of the cause restored the vision. Dermatitis from hatbands and bathing caps involve the area of the eyebrows and the upper lid. If the whole surfaces of both eyelids are affected, with or without the presence of conjunctival irritation, we should consider irritation from air-borne antigens, especially pollen and fungus spores. These lesions occur seasonally, but often remain present throughout the year because of secondary infection, or secondary sensitization with other contact agents. Food sensitization, as a rule, affects the lid margins. The nickel and plastic of glasses show characteristic patterns near the inner canthus of the eyes, on the bridge of the nose, and on both temples. This is so typical a localization that the diagnosis cannot be missed.

By determining the causes, however, we cannot always clear up the condition. A chronic lesion, as a rule, takes two to three weeks to heal after the cause is removed. However, most cases of dermatitis are complicated by either secondary infection or secondary contact sensitivity and, very often, by atopic sensitivity. Contrary to the general view on this subject, in my experience atopic sensitivity plays a very important part in many cases of contact dermatitis. We must frequently resort to injections of inhalants and to temporary food elimination in order to clear the lesions.

Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

BOVINE TETANUS ANTITOXIN

BOVINE tetanus antitoxin is now once more available! Allergists, especially pediatricians and internists, generally will welcome it after having practiced without it for almost four years.

The actions of manufacturers of pharmaceuticals are rarely the cause of editorial comment. In the case of Sharp and Dohme, however, the editors concurred that both publicity and commendation were due to the company for resuming production of tetanus antitoxin of the bovine type.

Sharp and Dohme was originally the only organization to manufacture the bovine type of tetanus antitoxin. The demand was never great. It was, however, constant. Allergists, awakened to the dangers of prophylactic horse serum injections, and doubly convinced of the necessity of using bovine serum in those patients with naturally acquired horse dander or artificially acquired horse serum sensitivity, needed to have the bovine serum on hand, however rarely.

With the advent of World War II, the demand, always small, began to diminish. In the armed forces alone over 20,000,000 people were actively immunized with toxoid and to so successful a degree that there were fewer than twenty cases of tetanus reported for all of the war period. The despeciated tetanus antitoxin was advanced as a prophylactic treatment, devoid of reaction potential. Experience proved it to be better than crude horse serum, but nevertheless it had to be used with caution in sensitive patients. Meanwhile, the possibility of controlling such reactions as might occur with so-called antihistaminic agents, and if necessary administering antibiotics prophylactically or therapeutically, appeared to change the treatment picture of tetanus.

But when all was said and all was done, there remained, to plague the allergist, a large number of patients who had not received toxoid and who had responded to the despeciated serum with true positive endermal and ophthalmic tests, after the false positive erythematous-edematous reactions had been ruled out. Treatment by the supposedly rapid desensitization procedure had few partisans. When combined with immediate toxoid injections and antibiotic therapy, all three left occasional patients, and almost all physicians, in a state of unhappy concern until all possibility of the development of tetanus was over. Although the dangers of acquiring tetanus were not exaggerated, the possible suffering curtailed could not be minimized. Those of us who, fortunately, had stocked up the lyophilized bovine-derived serum were much more tranquil in our minds.

(Continued on Page 809)

The Editor's Page

ANTIBIOTICS AND BRONCHIAL ASTHMA

THE FINAL WORD on whether antibiotics are, or are not, indicated in the treatment of bronchial asthma has not yet been said. Adding to the mutually contradictory reports in the literature is an excellent paper by Bupert,[1] who reports that, in fifty patients, asthmatic attacks (following acute respiratory infections) were relieved by penicillin. The author states that forty-seven (69 per cent) of sixty-eight asthmatic episodes were so controlled. Bupert feels that as initiating or prolonging causes of asthmatic episodes, respiratory infection plays a larger role than usually believed. He also considers that an infection is "almost solely responsible" for the occasional case of intractable asthma, refractory to "conventional anti-asthmatic procedures."

Proof that penicillin is excreted into the lung is demonstrated by the work of Matthews and Durie,[5] who collected seventy specimens of sputum from twenty patients with chronic bronchiectasis into whom had been injected sodium penicillin or penicillin LGl. The antibiotic was most readily detected in the sputum about three hours after the administration of single doses, but rarely after a dose of less than 300,000 units. With doses of 100,000 units given four-hourly or 500,000 units given every twelve hours, there was a reduction in the systemic disturbance and a change in the sputum from the yellow purulent type to white mucoid material. There was also a decrease in sputum volume. There was no difference noted in the therapeutic effects of the differing penicillin preparations.

One answer to the problem may lie in the fact that in so many pulmonary conditions exact diagnosis is not possible in early stages of the disease and that in the later stages seen in chronically affected patients the causative organisms may be many and varied in their effect. Combined antibiotic and sulfonamide therapy may perhaps be the solution. Gill[4] reports on the therapeutic results seen in patients with Friedlaender's pneumonia. Of eleven of his twenty-two patients who were treated with sulfonamides, three died, as did all of five given penicillin therapy. On the other hand, four given penicillin, streptomycin, and sulfonamides all recovered.

According to Walsh,[8] a fulminating case of Friedlaender's pneumonia, the organism of which on culture was resistant to penicillin and only moderately sensitive to Chloromycetin, responded with full recovery to the two drugs in combination.

Other indications that combined antibiotic and sulfonamide treatment is beneficial is shown by Walker,[7] who, in the treatment of lung abscess added sulfadiazine to the antibiotics given. Prigal[6] recommends the use of a bacitracin-penicillin aerosol in those patients in whom the offending organism does not respond to penicillin alone.

According to Davis,[2] the use of streptomycin and penicillin in patients with predominantly Gram-negative infection is successful by the aerosol method, using 0.3 to 0.5 gm of streptomycin with 150,000 units of penicillin in 0.75 to 1 cc of saline. Equally satisfactory, according to Farber and Ross[3] is 50,000 units of penicillin and 100 mg of streptomycin/cc saline.

All of these papers are steps toward the specific treatment of pulmonary infection, any of which may be the method of choice in helping the asthmatic patient in whom severe bronchospasm is associated with or follows such bacterial invasion. The reviewer of the recent literature feels that it will not be long before the problem is solved.

REFERENCES

1. Bupert, J. M.: Bull. School Med. Univ. Maryland, 36:115-118 (July) 1951.
2. Davis, D.: Arek. Otolaryng., 50:156, 1949.
3. Farber, J. E., and Ross, J.: California Med., 73:214, 1950.
4. Gill, J. R.: Am. J. M. Sc., 221-5, 1951.
5. Matthews, J. D., and Durie, T. B. M.: Lancet, 260:1417 (June 30) 1951.
6. Prigal, S. J.: J. Allergy, 22:50, 1951.
7. Walker, W. J.: New England J. Med., 241:266, 1949.
8. Walsh, J. M.: Brit. M. J., 2:1313, 1950.

ENDOCRINE HYPERSENSITIVITY

(Continued from Page 759)

lead to many interesting developments in the future and the solution of heretofore unsolved conditions.

REFERENCES

1. Baer, R. L., and Witten, V. H.: Skin tests with endocrine substances; method of Zondek and Bromberg. Ann. Allergy, 6:239 (May-June) 1948.
2. Goeckermann, W. H.: Hormonal therapy of acne vulgaris. Arch. Dermat. & Syph., 61:237 (Feb.) 1950.
3. Grollman, A.: Essentials of Endocrinology. P. 586. Philadelphia: J. P. Lippincott Co., 1947.
4. Hamilton, J.: Acne. J. Clin. Endocrinol., 2:636, 1942.
5. Hooker, C. W., and Pfeiffer, C. A.: Effects of sex hormones upon body growth, skin, hair and sebaceous glands in rat. Endocrinology, 32:69 (Jan.) 1943.
6. Lawrence, C. H., and Werthessen, N. T.: Treatment of acne with orally administered estrogens. J. Clin. Endocrinol., 2:636 (Nov.) 1942.
7. Urbach, E., and Gottlieb, P. M.: Allergy. New York: Grune and Stratton, 1943.
8. Way, S., and Andrews, G.: Hormones and acne. Arch. Dermat. & Syph., 61:584 (Apr.) 1950.
9. Zondek, B., and Bromberg, Y. M.: Endocrine allergy, allergic sensitivity to endogenous hormones. J. Allergy, 16:1 (Jan.) 1945.
10. Zondek, B., and Bromberg, Y. M.: Endocrine allergy, clinical reactions of allergy to endogenous hormones and their treatment. J. Obst. & Gynaec. Brit. Emp., 54:1 (Feb.) 1947.

213 Medical Arts Building

Progress in Allergy

BRONCHIAL ASTHMA

A Review of the Literature

MAURICE S. SEGAL, M.D., F.A.C.A., J. AARON HERSCHFUS, M.D., and ELLIOTT BRESNICK, M.D.

Physiologic Procedures in the Management of the Patient with Bronchial Asthma and Emphysema

THE respiratory dynamics of the acute asthmatic attack are similar in most respects to those occurring in chronic obstructive pulmonary emphysema. During the past several years striking advances have been made in our knowledge of the pathophysiology of pulmonary emphysema. Particularly valuable studies have appeared dealing with:

1. The divergence between the functional and histologic concepts of pulmonary emphysema, and the classification of pulmonary insufficiency based on lung volume measurements and gas exchange.[2,3,4,5]
2. Gas exchange across the alveolar membrane and the significance of the oxygen gradient between the alveoli and the arterial blood.[51,52,53]
3. The role of hypoxia and hypercapnia in the control of the medullary respiratory center and the aortic and carotid bodies.[22,66]
4. The role of oxygen therapy in correcting hypoxia and maintaining pulmonary ventilation.[12,13]
5. Other methods of correcting inadequate ventilation.[67,68]
6. The status of the heart and circulation in pulmonary emphysema based largely on cardiac catheterization studies.[29,36,42,43,62]

Some of these studies will be reviewed particularly in that they may offer a clearer concept of the physiologic management of the patient with severe bronchial asthma and pulmonary emphysema.

THE SIGNIFICANCE OF THE CHEMORECEPTOR CONTROL OF RESPIRATION UNDER CONDITIONS OF HYPOXIA

Comroe and Schmidt,[22] in discussing the part played by reflexes from the carotid body in the chemical regulation of respiration in the dog, stated that the carotid body "is only stimulated by anoxia of all degrees and even enormous increases in CO_2 tension do not appreciably depress it, whereas the cells of the center are depressed both by severe anoxia and by excessive hypercapnia."

The chief chemical regulator of the medullary respiratory center activity is the partial pressure of CO_2 (pCO_2). However, under conditions of hypoxia, the respiratory center is stimulated by reflexes arising in the sensory nerve endings in the aortic and carotid bodies. Bjurstedt[17] has ingeniously termed the sensitive respiratory stimulus due to pCO_2 the "centrogenic drive" and the respiratory stimulus arising in the aortic and carotid bodies (chemoreceptors) under conditions of hypoxia, the

From the Department of Inhalational Therapy, Boston City Hospital, and the Department of Medicine, Tufts College Medical School.

Doctor Segal is Clinical Professor of Medicine, Tufts College Medical School; Director, Department of Inhalational Therapy, Boston City Hospital.

Doctor Herschfus is Research Fellow in Medicine, Tufts College Medical School.

Doctor Bresnick is Assistant in Medicine, Tufts College Medical School.

"chemoreflex drive." Marshall and Rosenfield[41] found that animals given morphine or barbiturates stopped breathing when given oxygen because of the removal of the hypoxic stimuli responsible for the chemoreflex drive to the respiratory center. Schmidt and Comroe[57,58] postulated that under certain conditions (e.g., anesthesia) the control of breathing may be carried out by the chemoreceptors (Bjurstedt's[17] chemoreflex drive), which are responding to the arterial hypoxia, rather than the hypercapnia. Moreover, they then made the significant observation that the sudden relief of the hypoxia might be disastrously followed by respiratory failure.

HYPERCAPNIA IN BRONCHIAL ASTHMA AND EMPHYSEMA

The significance of hypoxia and hypercapnia in bronchial asthma and emphysema in the course of the disease and more particularly during oxygen therapy has been the subject of considerable discussion in recent years. The significance of the carbon-dioxide tolerance test in bronchial asthma and pulmonary emphysema has recently been subjected to considerable study.[26,27] It will be recalled that Scott[58] in 1920 first called attention to the relative insensitiveness of the respiratory regulating mechanism to carbon-dioxide excess in two patients with severe chronic pulmonary emphysema, and the role of anoxia as the primary stimulus to respiration. He attributed this loss of respiratory response to carbon dioxide, to the increased buffering action of the bicarbonates, and to the inability to increase adequately the tidal air and respiratory rate due to mechanical insufficiency of the chest. Donald and Christie[26] studied this phenomenon more extensively in a larger group of cases with adequate controls. They studied the ventilatory response to 4 per cent CO_2 in twenty-eight normal, twenty-three emphysematous, and seven asthmatic subjects. They also studied the effect on ventilation during the first five minutes of exposure to 12 per cent oxygen in ten emphysematous and eighteen normal subjects. They confirmed Scott's observations that the response to CO_2 is impaired in most emphysematous patients but could not attribute this tolerance to CO_2 to increased buffering (alkali reserve) or to adaptation of the respiratory center or to the relative immobility of the chest. On the other hand, the asthmatic patients (without emphysema) all demonstrated normal reactions during the first five minutes of exposure to 4 per cent CO_2. The effect of anoxia on ventilation was very similar in the CO_2-tolerant emphysematous subjects and the normal controls. Donald[27] applied the CO_2 tolerance test to a group of miners with pneumoconiosis. He found impaired tolerance (loss of sensitivity) only in those cases who were dyspneic with evidence of emphysema. A number of subjects with dyspnea and no evidence of emphysema were sensitive to CO_2 inhalations. He concluded that in this group the dyspnea was due to unknown factors other than emphysema. To come to this conclusion, one would have to accept the increased CO_2 tolerance as specific for emphysema.

THE EFFECTS OF OXYGEN THERAPY ON THE ARTERIAL OXYGEN AND CARBON-DIOXIDE CONTENT IN BRONCHIAL ASTHMA AND PULMONARY EMPHYSEMA

In 1921, several significant papers appeared describing the improvement in arterial hypoxia and rise in the arterial carbon-dioxide content in patients with bronchial asthma and pulmonary emphysema following oxygen therapy. Meakins[44] observed that arterial hypoxia and arterial hypercapnia occur during the asthmatic attack, and that a rise in arterial oxygen concentrations follows oxygen therapy. Barach and Woodwell[6] observed in some patients with pulmonary emphysema an increase in the arterial carbon-dioxide content during and after breathing 50 to 100 per cent concentrations of oxygen. These authors also reported respiratory acidosis and high elevation of CO_2 content in two patients with shallow breathing due to lethargic encephalitis, who were treated with high concentrations of oxygen. These were

probably the first recorded cases of elevated arterial CO_2 content attributed to oxygen therapy. Barach and Richards,[7] and Richards and Barach[50] subsequently observed, during the course of oxygen therapy in patients with heart disease and pulmonary fibrosis secondary to tuberculosis, an increased arterial oxygen saturation and also a remarkable elevation of the arterial carbon-dioxide content. They considered the latter entirely a compensatory adaptation ensuing upon the decreased pulmonary ventilation and thought that this also allowed a normal excretion of CO_2 with a smaller effective tidal volume.

DANGERS OF THE USE OF HIGH CONCENTRATIONS OF OXYGEN IN CHRONIC PULMONARY EMPHYSEMA

(a) Dead Space-like Ventilation. (b) Venoarterial Shunts

Particular emphasis continues to appear concerning the hazards of employing oxygen in concentrations above 50 per cent in patients with chronic pulmonary emphysema and pulmonary heart disease. In these patients the arterial hypoxia is usually accompanied by an elevated arterial pCO_2 (hypercapnia), which is direct evidence of the defective gas exchange and a tendency for a decrease in the arterial pH (respiratory acidosis). The patient attempts to compensate by hyperventilation and blowing off the CO_2. If hyperventilation of a sufficient number of normally ventilating alveoli (free of obstruction) and well perfused alveoli occurs (normal distribution factor), then carbon-dioxide retention will not take place. On the other hand, if hyperventilation does not affect sufficient numbers of normal alveoli, carbon-dioxide retention occurs. Such inadequate ventilation has been termed "dead space-like ventilation" by West et al.[66] On the other hand, the existing arterial hypoxia cannot be corrected to any significant degree by the above-described compensatory hyperventilation. Perfusion of poorly ventilated alveoli results in arterial hypoxia as well as CO_2 retention. The inadequately oxygenated blood from these alveoli, mixing with the remainder of the capillary blood, creates a virtual veno-arterial shunt.[4,5,66] Riley and others[39,51,52,53] have been able to calculate the magnitude of such shunts.

THE PATHOPHYSIOLOGY OF THE SYNDROME OF CARBON-DIOXIDE EXCESS

Barach et al[7,8,11,13] and Comroe et al[23,24] noted that in patients with chronic hypoxia associated with elevated arterial CO_2 content and respiratory acidosis, high concentrations of oxygen occasionally were followed by distressing central nervous symptoms culminating in coma.

Recent studies, which will be discussed, have shed further light on the state of carbon-dioxide excess which may follow the use of high concentrations of oxygen in patients with chronic pulmonary emphysema and clearly differentiate this syndrome from other types of oxygen toxicity as seen (1) in normal subjects, (2) in patients receiving 100 per cent concentrations without interruption over long periods, and (3) in patients who are inadvertently inhaling excessive concentrations of CO_2 while receiving adequate oxygen therapy. Comroe et al[23,24] and others have described direct and indirect effects of high concentrations of oxygen *in normal subjects:* namely, irritation of the pulmonary parenchyma, drop in vital capacity, and increased amplitude in breathing.

Discussions of the potential hazards of high concentrations of oxygen in patients with chronic pulmonary emphysema have also been presented in recent reports on the pathophysiology of pulmonary emphysema by Comroe et al,[24] West et al,[66] and Whittenberger et al.[18,68] It would appear that in the compensated phase of chronic pulmonary emphysema, the high pCO_2 serves as an increased centrogenic drive to cause hyperventilation at rest despite the possible presence of hypoxia.[3,4,5] During physical activity the increased arterial hypoxia with its homeostatic chemoreflex drive may be responsible for the hyperventilation.[66] When the ventilatory capacity is reduced (viz., infection and bronchoconstrictor influences), it may be unable to

maintain the compensatory hyperventilation called forth by either the centrogenic or chemoreflex drive. This leads to further CO_2 retention and possibly a state of CO_2 narcosis, wherein the centrogenic drive no longer stimulates the respiratory center and ventilation is reduced still further. The CO_2 retention brings about an increase in the alkali reserve and a fall in serum chlorides.[7] Ultimately respiratory ventilation is controlled largely by the hypoxic-chemoreflex drive and hypoventilation is then observed.[2,3,4,5]

Barach et al[7,8,11,13] interpreted this syndrome by stressing that the irrationality, delirium, or coma which may follow the use of high concentrations of oxygen in these patients is not only preventable by the graded program of oxygen administered, but is also not due to the rise in CO_2 tension alone unless it is associated with an acid shift in pH. With regulated oxygen therapy (one liter per minute daily with one liter flow increases at two- or three-day intervals, until seven liters per minute is administered), he[13] has seen the arterial CO_2 content rise to 100 and 132 volumes per cent with a normal pH, relief of dyspnea, and normal mental functioning. It will be recalled that CO_2 output depends on the alveolar pCO_2. Inasmuch as this can be lowered by hyperventilation, the CO_2 output can be increased in the absence of pulmonary fibrosis. Barach has repeatedly stressed that the increased pCO_2 (arterial and alveolar) functions in a homeostatic manner by exhaling CO_2 in relatively high concentrations, as well as by retaining base and excretion of chlorides. Others[2,3,4,5,18,24,66] have attributed most of the deleterious effects to the pCO_2. Barach[9,13] also feels that acclimatization to the increased oxygen tension may be observed with improvement in central nervous system effects. He stresses the need for oxygen and expresses less concern for the CO_2 retention; for he believes that the alveolar CO_2 elimination will keep pace with the rise in arterial pCO_2, as long as there is a *gradual* reduction in pulmonary ventilation associated with oxygen therapy. Barach[13] also has noted benefit with the use of intravenous sodium lactate when respiratory acidosis occurred. He reported the occurrence of coma in a patient with pulmonary emphysema treated with oxygen, who recovered during the continuous administration of oxygen. Davies and MacKinnon,[25] on the other hand, reported a fatality. Their patient with chronic cor pulmonale was given oxygen by B.L.B. mask. He became comatose and died four hours after oxygen was given. However, the patient also received 10 per cent CO_2 to stimulate respiration.

Beale et al[15] recently stressed that this syndrome of carbon-dioxide excess observed in emphysema can occur in the course of oxygen therapy in bronchial asthma complicated by respiratory acidosis. They described in detail a case history, including arterial blood gas and pH determinations and pulmonary function studies. The low arterial oxygen saturation and high index of intrapulmonary mixing would indicate hypoxic emphysema, according to Baldwin's classification.[4,5] On three occasions the patient became unconscious while being treated with oxygen. The respiratory acidosis was aggravated with breathing of oxygen. He was also given barbiturates for sedation. There was no pulmonary function evidence of pulmonary emphysema or fibrosis after recovery. The reversibility of the pulmonary function changes may possibly reflect the efficacy of ACTH in this patient. Lukas[40] recently stated that ACTH and cortisone produced far more striking changes in the pulmonary function of cases of long-standing chronic bronchiolar obstruction with secondary emphysema than those effected by conventional bronchodilators. Schiller et al[55] subsequently reported a similar paradoxical response to oxygen in another patient with severe chronic bronchial asthma, respiratory acidosis, hypoxic emphysema, and bronchiectasis. The authors urged laboratory or clinical observations during the administration of air and oxygen, as a guide for oxygen therapy in patients with bronchial asthma and respiratory acidosis.

A working knowledge of these homeostatic mechanisms is essential in the physiologic management of the patient with respiratory embarrassment associated with

severe bronchial asthma (hypoxic emphysema) or chronic pulmonary emphysema. The sudden administration of oxygen in high concentrations in an attempt to relieve dyspnea, hypoxia, and cyanosis may be followed by a breakdown in the homeostatic chemoreflex drive sustaining respiration. The increased arterial oxygen content removes the hypoxic stimulus to the chemoreceptors—aortic and carotid bodies (the chemoreflex drive mechanism)—and this may result in further hypoventilation,[66] greater CO_2 retention, and ultimately respiratory acidosis with a drop in arterial pH. Indeed weakness, headaches,[19] air hunger, neurological manifestations, drowsiness, coma, and delirium have been observed to occur progressively under such conditions. A rise in cerebrospinal pressure[25] and papilloedema[63] have been observed in such patients. Comroe et al[24] suggested that many factors were responsible for the central nervous system symptomatology; namely, carbon-dioxide narcosis, depression of the cerebral cortex by high oxygen tension both directly and indirectly, and increased cerebrospinal-fluid pressure. More recently Patterson et al[48] concluded that the elevation in arterial pCO_2, rather than the elevation in pO_2 was responsible for the elevation of the cerebral blood flow (CBF) and some of the mental changes observed in patients with emphysema receiving oxygen therapy. They carried out careful control studies. These studies should serve to caution the overzealous therapeutist to avoid *the sudden administration of high concentrations of oxygen* to the hypoxic patient with severe bronchial asthma or pulmonary emphysema, particularly if ventilation is already depressed by respiratory-depressing drugs such as morphine, the barbiturates, anesthetic agents, et cetera. Further depression of respiration and central nervous system disturbances may follow. This syndrome will probably be observed only rarely in bronchial asthma, unless respirations are depressed or severe functional emphysema is present.

Recent studies have re-emphasized that it is not enough to administer oxygen to the hypoxic patient. The entire transportation system should be analyzed and the deficiency corrected. Removal and treatment of the cause; supplemental therapy of shock, restoration of hemoglobin, blood plasma[62] and electrolytes;[58] regulation of acid-base balance;[13] and avoidance of continuous inhalation of CO_2[13] in concentrations above 1.0 per cent are as important as the choice of the exact concentration of oxygen to be delivered and the apparatus employed. Practical evaluation of these factors was made, and therapeutic suggestions were outlined for the management of the seriously ill asthmatic patient.[12,62]

THERAPEUTIC IMPLICATIONS

The therapeutic implications of these observations, as well as others to be referred to, in the management of seriously ill patients with chronic bronchial asthma associated with severe functional or organic emphysema and chronic hypertrophic pulmonary emphysema with hypoxia, will now be presented:

1. *Respiratory center depressing drugs* should be avoided in these patients, e.g., barbiturates, morphine and depressing anesthetic agents, particularly nitrous oxide.[41,56,57] Caffeine sodium benzoate may be used if respiration is depressed.

2. *Oxygen should be administered in low concentrations,* gradually increasing the concentrations by nasal catheter;[9,11,13] or by the use of plastic face tents of known performance.[60] There should also be a gradual reduction in oxygen concentration at the conclusion of therapy.

It should be stressed that the above discussions of the hazards of the sudden administration of high concentrations of oxygen, namely, a further depression of an inadequate form of respiration, are limited only to some patients with chronic pulmonary emphysema, severe bronchial asthma, and hypoxic emphysema, barbiturate intoxication or anesthesia, with concomitant evidence of arterial hypoxia, elevated

arterial pCO_2, and respiratory acidosis. Inhalations of 50 per cent oxygen, without preliminary progressive increases, may be given safely to patients with bronchial asthma or pulmonary emphysema who have no pre-existing arterial anoxia and cyanosis.[60] High concentrations of oxygen are indicated and may be administered in a number of clinical entities: particularly pulmonary edema, atelectasis, pneumonia, carbon monoxide poisoning, et cetera. Methods of administration and the technique have been defined by Andrews,[1] Barach,[12] Segal[62] and others.

3. *The physician should make certain that concomitant CO_2 inhalation* of concentrations above 1.0 per cent from rebreathing for long periods is avoided.[12,13] Scott[58] and Donald and Christie[26] demonstrated the diminished response to CO_2 inhalations in the emphysematous patient, and Ivy et al[38] recently demonstrated the depressant ventilatory effect of CO_2 inhalations in the hypoxic animal.

4. When hypoventilation, respiratory acidosis, and severe CO_2 retention appear, the use of *mechanical respiration*[18] should be considered (masks, chambers, and electrophrenic stimulation). Motley et al[45,46,47] and Gordon et al[35] have described the successful use of oxygen with the intermittent positive pressure respirator in preventing serious CO_2 retention in these patients. They obtained intermittent positive pressure by using a cycling valve with maximum peak pressures at the mouth adjustable from 0 to 30 cm of water. They usually employed 100 per cent oxygen with simultaneous aerosols of Vaponefrin and Neosynephrin. The treatments were given two or three times daily for the acute episodes and two or three times weekly for the chronic manifestations. Each treatment took fifteen minutes. They noted great benefit in their patients, particularly in the relief of dyspnea and improvement in bronchial drainage. Reiser and Ferris[49] treated three intractable asthmatic patients by employing the Drinker respirator as a possible aid for inspiration and as positive pressure to the chest wall and abdomen during expiration. Adequate oxygenation was maintained and partial anesthesia was recommended in order to quiet the patient sufficiently to coöperate. Dramatic disappearance of cyanosis, improvement in circulation, and relief from anoxia were observed. Unfortunately, an unfavorable outcome occurred in two patients. The principle of the substitution of an artificial mechanism to replace some of the muscular effort of the asthmatic subject appears sound. The major difficulty of synchronizing the patient's respirations with the cycle of the respirator may possibly be overcome with the use of the new Emerson type respirator[28] designed essentially with this problem in mind.

Whittenberger et al, in a series of comprehensive papers,[18,54,67,68] discussed the pathophysiology of various types of respiratory failure and their treatment. Their particularly lucid discussion of the use of positive pressure breathing, oxygen therapy, resuscitation methods, tank respirators, and electrophrenic respiration should be studied by those intimately involved in the management of pulmonary failure. The possible value of electrophrenic respiration[67,68] as a help in re-educating the diaphragm of the emphysematous patient is most intriguing.

The same authors applied their principles of mechanical ventilation, particularly electrophrenic respiration, in the management of the hypoventilation syndrome sometimes observed in the course of bulbar poliomyelitis.[54] They suggest that the altered sensitivity (insensitive) of the respiratory center to carbon dioxide is consequent to medullary involvement by the disease. Oxygen therapy could be responsible for further respiratory depression and further elevation of the pCO_2 in the medullary centers to the point of narcosis. Induced adequate respiration (electrophrenic) tends to reverse the above pattern and partially restores the sensitivity of the respiratory center. The hazards of oxygen therapy would then be eliminated.

5. One should be prepared to institute *pneumoperitoneum therapy* in the seriously ill patient with anoxic emphysema who fails to respond to conservative measures. More adequate elimination of CO_2 should follow with improvement in ventilation.

Wright et al[69] made a study of the physiological effects of pneumoperitoneum upon the respiratory apparatus. In a careful study on a limited number of patients, they were able to demonstrate a marked reduction in the functional residual capacity, residual volume, and total lung capacity in the erect position, and to a lesser degree in the recumbent position. They concluded that pneumoperitoneum, when fully established, was an effective method of reducing distention of the lung. Gaensler and Carter[21,31] recently made a comprehensive study of the pulmonary functions and volumes in thirteen patients with far advanced pulmonary emphysema before and after pneumoperitoneum treatment. Ten of the thirteen patients reported improvement in symptomatology, which increased with lengthened time of treatment. A marked increase in diaphragmatic motion was observed after treatment. A striking reduction in residual volume was the most significant pulmonary function improvement. Respiratory gases (percentage oxyhemoglobin saturation and carbon-dioxide tension) were studied before and after treatment in three patients.[31] A striking increase in oxygen saturation and reduction in carbon-dioxide tension, particularly in the after-exercise values, was noted in one patient after pneumoperitoneum. A recent report by Furman and Callaway[30] gives further evidence of the usefulness of this form of therapy in a significant number of patients with pulmonary emphysema.

Callaway and McKusick[20] recently made a significant contribution in reporting two patients with the syndrome of carbon-dioxide intoxication (venous blood determinations) progressing to coma, which they considered profound manifestations of pulmonary emphysema. The first patient failed to respond to oxygen, aminophylline, digitalis, and penicillin therapy. Autopsy revealed hypertrophy of both ventricles, consolidation of the left lower lobe, pulmonary emphysema, and blebs. The second patient also failed to respond to oxygen, aminophylline intravenously, adrenaline, and attempts to correct the low serum chlorides. He was placed in a Drinker-Emerson respirator in an attempt to produce more adequate ventilation and was also given nasal oxygen. Despite these procedures, he developed marked cyanosis and coma. The respirator appeared to be ineffective in producing adequate movements of the chest cage and diaphragm. Striking improvement was observed with the successful institution of a pneumoperitoneum. An additional refill was given six hours later. There was a marked drop in CO_2 combining power, return of cough mechanism, and clearing of sensorium. Fluoroscopy, two weeks later, revealed good diaphragmatic excursions. The authors also stressed the necessity for sodium chloride therapy to re-establish acid-base balance. They favored the theory of CO_2 narcosis[24] to the theory of depression of the pH[13] as the cause for the mental changes. Calloway and McKusick[20] stated that they did not observe oxygen acclimatization in these two patients as described by Barach et al.[9,13] However, to accomplish acclimatization, oxygen should be administered in lower concentrations with slow, progressive increase in the concentrations. The authors further point out the difficulty in synchronizing the patient's attempts at respiration with the cycle of the Drinker respirator. Finally, the authors[20] make the important contribution of urging pneumoperitoneum therapy when all other therapeutic measures have failed. The elevation of the diaphragm and the reduction of the residual volume/total lung capacity ratio promote an increase in the effective tidal air volume and reduction of the inadequately ventilating portions of the lungs, with the ultimate elimination of larger amounts of carbon dioxide. They call attention to the fact that the electrolyte disturbance will probably recur unless there is an improvement in the pulmonary ventilation.

6. *Breathing Exercises.*—Gay[32] emphasizes the dramatic benefits that may follow breathing exercises, both active and passive, which are designed to reduce the over-

distended lungs in bronchial asthma and pulmonary emphysema. He describes several of these procedures with good picture illustrations. He emphasizes that we have fallen behind our English and South American colleagues in our attempts to restore the general health of asthmatic patients, particularly children. One should be able to prevent the disabling kyphoscoliosis that develops in some of these patients. Barach[11] recently emphasized the importance of developing diaphragmatic breathing in patients with pulmonary emphysema by special training and daily practice. He teaches the patient to lower the diaphragm, manifested by protrusion of his abdomen during inspiration, and to press with both hands inward and upward during the latter third of expiration. These procedures tend to restore the lost diaphragmatic excursions. The expiratory phase may be carried out for the sick patient passively and may help in eliminating trapped air. The lips may also be kept pursed in expiration. Gordon et al[34,35] advocate the wearing of special abdominal support to obtain abdominal compression necessary to elevate the diaphragm to the levels of expiration. Improved ventilatory function and a more useful coughing mechanism may follow.

The implications of diaphragmatic breathing exercises, abdominal support, and pneumoperitoneum as important forms of therapy in the chronic asthmatic patient with secondary emphysema are clear. In patients with severe emphysema, secondary to chronic bronchial asthma, we generally advocate breathing exercises designed to improve the spine and chest relationships, as well as diaphragmatic function, along with abdominal belts and skeletal support (orthopedic braces) when indicated, e.g. kyphoscoliosis, and ultimately pneumoperitoneum.

7. *The Use of Aminophylline.*—The evidence continues to accumulate proving the efficacy of aminophylline in relieving acute bronchospastic crises and the state of chronic bronchospasm occurring in bronchial asthma and chronic pulmonary emphysema. Segal et al[37,62] demonstrated that aminophylline exerts an appreciable antihistaminic effect but a very moderate anticholinergic effect in protecting against histamine and methacholine-induced dyspnea and bronchospasm in asthmatic subjects. Truitt et al,[64] employing a quantitative technique, studied the effective blood levels of aminophylline obtained by various routes of administration. Their results[64] were comparable to those obtained with the protection study technique.[37,62] They concluded[64] that blood levels of 0.5 mg. per cent were necessary for therapeutic effects.

Various routes of administration continue to be employed. The continuous intravenous technique has been described by many investigators.[33,62] The technique of combining aminophylline and ACTH in the form of a continuous intravenous infusion during the control period of the status asthmaticus state was recently stressed.[61] The value of the use of solutions of aminophylline via rectal administration for the chronic asthmatic patient, described by Barach,[10] has been confirmed by others.[59,62] There continue to appear a variety of oral medications combining aminophylline (or similar derivatives) with ephedrine (or similar derivatives) and some form of sedation for the relief or prevention of the mild but chronic asthmatic attack. The difficulty with most of these preparations appears in their side reactions, when dosages of aminophylline are employed which are necessary to achieve therapeutic results. The addition of antinausea factors (local and central) to aminophylline* has recently made it possible to administer the amount of aminophylline required for good therapeutic effect, with or without the addition of ephedrine or a barbiturate. Symptoms of nausea occurred in only two instances in a series of 100 patients with bronchial asthma and pulmonary emphysema who were given Dainite® tablets on arising and retiring.[14] Good clinical tolerance,[14,61] adequate protection against the

*Dainite® Tablets, Irwin, Neisler & Co., Decatur, Illinois.

effects of experimentally induced asthmatic crises,[62] and improvement in pulmonary function have been observed.[16] Adequate theophylline blood levels after insufflation of micronized aminophylline powder were observed in a recent study in rabbits.[65] Herschfus et al,[37] on the other hand, observed no adequate protection by aerosol administration of aminophylline against experimentally induced bronchoconstriction in asthmatic subjects. Clinical experience will ultimately decide the value of the aerosol route for aminophylline in bronchial asthma.

8. *The Use of Digitalis.*—The clinician is frequently faced with the problem of deciding whether to use digitalis in the severely hypoxic patient with bronchial asthma or pulmonary emphysema. Conclusive evidence of cor pulmonale or heart failure is frequently missing. McMichael and Sharpey-Schafer[42,43] first demonstrated that patients with cor pulmonale, with or without heart failure, may have a high cardiac output. The recent work by Ferrer et al[29] and Harvey et al[36] has stressed that in patients with chronic cor pulmonale and emphysema, an increased cardiac output type of heart failure is generally found. However, in their patients with silicosis and emphysema, the cardiac output was not elevated.[36] These investigators also pointed out that the hypoxia was directly or indirectly responsible for the circulatory complications found in these patients, and that these complications are generally reversible. They recommend digitalis for the failing right ventricle despite the increased cardiac output. In addition, they stress the need for venesection to reduce the elevated blood volume, bronchodilator aerosols to relieve the bronchoconstriction, antibiotics, and the judicious use of oxygen to relieve the basic hypoxia.[36] Zimmerman[70] also found both increased and decreased types of cardiac output in his patients with emphysema. Gordon et al[35] found drug treatment for emphysema disappointing. They found some benefit from digitalis and theobromine derivatives in failure of the circulation due to primary myocardial disease, but of no use in cor pulmonale.

The effects of bronchial asthma on the cardiovascular system are largely the effects of emphysema. On several occasions,[59,62] we have felt that seriously ill patients with bronchial asthma and evidence of cor pulmonale were not helped or possibly were made worse by digitalization. They appeared to be helped more by oxygen administration and the rigid use of a salt-free regimen and mercurials.

REFERENCES

1. Andrews, A. H., Jr.: Oxygen Therapy Techniques Including Carbon Dioxide, Helium and Water Vapor. Chicago: Year Book Publishers, 1943.
2. Baldwin, E. de F.; Cournand, A.; and Richards, D. W., Jr.: Pulmonary insufficiency. I. Physiological classification, clinical methods of analysis, standard values in normal subjects. Medicine, 27:243, 1948.
3. Baldwin, E. de F.; Cournand, A.; and Richards, D. W., Jr.: Pulmonary insufficiency. II. A study of thirty-nine cases of pulmonary fibrosis. Medicine, 28:1, 1949.
4. Baldwin, E. de F.; Cournand, A.; and Richards, D. W., Jr.: Pulmonary insufficiency. III. A study of 122 cases of chronic pulmonary emphysema. Medicine, 28:201, 1949.
5. Baldwin, E. de F.; Harden, K. A.; Greene, D. G.; Cournand, A.; and Richards, D. W., Jr.: Pulmonary insufficiency. IV. A study of 16 cases of large pulmonary air cysts or bullae. Medicine, 29:169, 1950.
6. Barach, A. L., and Woodwell, M. N.: Studies in oxygen therapy with determinations of blood gases. I. In cardiac insufficiency and related conditions. Arch. Int. Med., 28:367, 1921.
7. Barach, A. L., and Richards, D. W., Jr.: Effects of treatment with oxygen in cardiac failure. Arch. Int. Med., 48:325, 1931.
8. Barach, A. L.: Effect of low and high oxygen tensions on mental functioning. J. Aviation Med., 12:30, 1941.
9. Barach, A. L.; Eckman, M.; Tribe, E.; Oppenheimer, C. R., Jr.; and Soroka, M.: Observations on methods of increasing resistance to oxygen poisoning and studies of accompanying physiological effects. Am. J. Physiol., 142:462, 1944.

10. Barach, A. L.: Rectal instillation of aminophylline in intractable asthma. J.A.M.A., 128:589, 1945.
11. Barach, A. L.: Physiological treatment of pulmonary emphysema. Am. Pract., 2:771, 1948.
12. Barach, A. L.: Physiologic Therapy in Respiratory Diseases, 2nd Ed. Philadelphia: J. B. Lippincott & Co., 1948.
13. Barach, A. L.: Treatment of anoxia in clinical medicine. Bull. N. Y. Acad. Med., 26:370, 1950.
14. Barach, A. L.: Remissions in bronchial asthma and pulmonary emphysema. J.A.M.A.: To be published.
15. Beale, H. D.; Schiller, I. W.; Halperin, M. H.; Franklin, W., and Lowell, F. G.: Delirium and coma precipitated by oxygen in bronchial asthma complicated by respiratory acidosis. New England J. Med., 244:710, 1951.
16. Bickerman, H. G.; Hylan, G.; and Beck, G.: Personal Communication.
17. Bjurstedt, A. G. H.: Interaction of centrogenic and chemoreflex control of breathing during oxygen deficiency at rest. Acta Physiol. Scandinav. (suppl. 38), 12:1, 1946.
18. Boutourline-Young, H. J., and Whittenberger, J. L.: The use of artificial respiration in pulmonary emphysema accompanied by high carbon dioxide levels. J. Clin. Investigation, 30:838, 1951.
19. Brazier, M. A. B.: Physiological effects of carbon dioxide on activity of central nervous system in man with special reference to problem of high altitude flying: review. Medicine, 22:205, 1943.
20. Callaway, J. J., and McKusick, V. A.: Carbon-dioxide intoxication in emphysema; emergency treatment by artificial pneumoperitoneum. New England J. Med., 245:9, 1951.
21. Carter, M. G.; Gaensler, E. A.; and Kyllonen, A.: Pneumoperitoneum in the treatment of pulmonary emphysema. New England J. Med., 243:549, 1950.
22. Comroe, J. H., Jr., and Schmidt, C. F.: Part played by reflexes from carotid body in chemical regulation of respiration in dog. Am. J. Physiol., 121:75, 1938.
23. Comroe, J. H., Jr.; Dripps, R. D.; Dumke, P. R.; and Deming, M.: Oxygen toxicity: effect of inhalation of high concentrations of oxygen for twenty-four hours on normal men at sea level and at simulated altitude of 18,000 feet. J.A.M.A., 128:710, 1945.
24. Comroe, J. H., Jr.; Bahnson, E. R.; and Coates, E. O., Jr.: J.A.M.A., 143:1044, 1950.
25. Davies, C. E., and MacKinnon, J.: Neurological effects of oxygen in chronic cor pulmonale. Lancet, 2:883, 1949.
26. Donald, K. W., and Christie, R. V.: The respiratory response to carbon dioxide and anoxia in emphysema. Clin. Sc., 8:33, 1949.
27. Donald, K. W.: Reaction to carbon dioxide in pneumoconiosis of coal miners. Clin. Sc., 8:45, 1949.
28. Emerson, J. H., Manufacturer, Cambridge, Mass.: personal communication.
29. Ferrer, M. I.; Harvey, R. M.; Cathcart, R. T.; Webster, C. A.; Richards, D. W., Jr.; and Cournand, A.: Some effects of digoxin upon the heart and circulation in man. Digoxin in chronic cor pulmonale. Circulation, 1:161, 1950.
30. Furman, R. H., and Callaway, J. J.: Artificial pneumoperitoneum in treatment of pulmonary emphysema: preliminary report. Dis. of Chest, 18:232, 1950.
31. Gaensler, E. A., and Carter, M. G.: Ventilation measurements in pulmonary emphysema treated with pneumoperitoneum. J. Lab. & Clin. Med., 35:945, 1950.
32. Gay, L. N.: Diagnosis and Treatment of Bronchial Asthma. Baltimore: Williams-Wilkins Co., 1946.
33. Goodall, R. J., and Unger, L.: Continuous aminophyllin therapy in status asthmaticus. Ann. Allergy, 5:190, 1947.
34. Gordon, B.: Mechanism and use of abdominal supports and treatment of pulmonary diseases. Am. J. M.Sc., 187:692, 1934.
35. Gordon, B.; Motley, H. L.; Theodos, P. A.; and Lang, L. P.: Physiological aspects and treatment of emphysema. Geriatrics, 5:303, 1950.
36. Harvey, R. M.; Ferrer, M. I.; Richards, D. W., Jr.; and Cournand, A.: Influence of chronic pulmonary disease on the heart and circulation. Am. J. Med., 10:719, 1951.
37. Herschfus, J. A.; Rubitsky, H. J.; Beakey, J. F.; Bresnick, E.; Levinson, L.; and Segal, M. S.: Evaluation of therapeutic substances employed for the relief of bronchial asthma. Int. Arch. of Allergy and Applied Imm., 2:97, 1951.

38. Ivy, J. H.; Grodins, F. S.; Adler, H. F.; and Snapp, F. E.: Studies on asphyxia; effects of CO_2 inhalation on anoxic animal. J. Aviation Med., 18:577, 1947.
39. Lilienthal, J. L., Jr.; Riley, R. L.; Proemmel, D. D.; and Franke, R. E.: An experimental analysis in man on the oxygen pressure gradient from alveolar air to arterial blood durjng rest and exercise at sea level and at altitude. Am. J. Physiol., 147:199, 1946.
40. Lukas, D. S.: Pulmonary function in a group of young patients with bronchial asthma. J. Allergy, 22:411, 1951.
41. Marshall, E. K., Jr., and Rosenfeld, M.: Depression of respiration by oxygen. J. Pharmacol. & Exper. Therap., 57:437, 1936.
42. McMichael, J., and Sharpey-Schafer, E. P.: The action of intravenous digoxin in man. Quart. J. Med., 13:123, 1944.
43. McMichael, J.: Study of circulatory failure by venous catheterization. Advances in Internal Medicine, 64. New York: Interscience Publishers, Inc., 1947.
44. Meakins, J.: Observations on the gases in human arterial blood in certain pathological pulmonary conditions and in their treatment with oxygen. J. Path. & Bact., 24:79, 1921.
45. Motley, H. L.; Cournand, A.; Eckman, M.; and Richards, D. W.: Physiological studies on man with the pneumatic balance resuscitator "Burns Model." J. Aviation Med., 17:431, 1946.
46. Motley, H. L.: The use of oxygen in comatose states. Bull. New York Acad. Med., 26:479, 1950.
47. Motley, H. L., and Tomashefski, J. F.: Effect of high and low oxygen levels and intermittent positive pressure breathing on oxygen transport in lungs in pulmonary fibrosis and emphysema. J. Applied Physiol., 3:189, 1950.
48. Patterson, J. L., Jr.; Heyman, A.; and Duke, T. W.: Effects of oxygen therapy on cerebral functions in patients with chronic pulmonary emphysema. Am. J. Med., 11:249, 1951.
49. Reiser, M. F., and Ferris, E. B., Jr.: Observations on the use of the respirator in refractory status asthmaticus. Ann. Int. Med., 29:64, 1948.
50. Richards, D. W., Jr., and Barach, A. L.: The effects of oxygen treatment over long periods of time in patients with pulmonary tuberculosis. Am. Rev. Tuberc., 26:253, 1932.
51. Riley, R. L., and Cournand, A.: "Ideal" alveolar air and the analysis of ventilation-perfusion relationships in the lungs. J. Applied Physiol., 1:825, 1949.
52. Riley, R. L.: Pulmonary gas exchange. Am. J. Med., 10:210, 1951.
53. Riley, R. L.; Cournand, A.; and Donald, K. W.: Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs. J. Applied Physiol., 4:102, 1951.
54. Sarnoff, S. J.; Whittenberger, J. L.; and Affeldt, J. E.: Hypoventilation syndrome in bulbar poliomyelitis. J.A.M.A., 147:30, 1951.
55. Schiller, I. W.; Beale, H. D.; Franklin, W.; Lowell, F. C.; and Halperin, M. H.: The potential danger of oxygen therapy in severe bronchial asthma. J. Allergy, 22:423, 1951.
56. Schmidt, C. F., and Comroe, J. H.: The role of the carotid and aortic bodies in the defense of the mammalian organism against oxygen lack. Science, 92:510, 1940.
57. Schmidt, C. F., and Comroe, J. H.: Functions of the carotid and aortic bodies. Physiol. Rev., 20:115, 1940.
58. Scott, R. W.: Observations on pathologic physiology of chronic pulmonary emphysema. Arch. Int. Med., 26:544, 1920.
59. Segal, M. S.: Facts and fancies in the management of the seriously ill patient with bronchial asthma. Dis. of Chest, 14:795, 1948.
60. Segal, M. S., and Herschfus, J. A.: Oxygen Therapy. Description of a new face tent. In Press.
61. Segal, M. S., and Hershfus, J. A.: Intravenous ACTH therapy in the treatment of bronchial asthma. Dis. of Chest: to be published.
62. Segal, M. S.: The Management of the Patient with Severe Bronchial Asthma. Springfield, Ill.: Charles C Thomas Co., 1950.
63. Simpson, T.: Papilloedema in emphysema. Brit. M. J., 2:639, 1948.
64. Truitt, E. B., Jr.; McKusick, V. A.; and Krantz, J. C.: Theophylline blood levels after oral, rectal and intravenous administration, and correlation with diuretic actions. J. Pharmacol. & Exper. Therap., 100:309, 1950.
65. Waxler, S. H., and Moy, H. B.: Theophylline blood levels after insufflation of micronized aminophylline powder. J. Allergy, 22:434, 1951.

66. West, J, R.; Baldwin, E. de F.; Richards, D. W., Jr.; and Cournand, A.: Physiopathologic aspects of chronic pulmonary emphysema. Am. J. Med., 10: 481, 1951.
67. Whittenberger, J. L.; Sarnoff, S. J.; and Hardenbergh, E.: Electrophrenic respiration. II. Its use in man. J. Clin. Investigation, 28:124, 1949.
68. Whittenberger, J. L., and Sarnoff, S. J.: Physiologic principles in the treatment of respiratory failure. M. Clin. North America, Sept.: 1335, 1950.
69. Wright, G. W.; Place, R.; and Princi, F.: The physiological effects of pneumoperitoneum upon the respiratory apparatus. Am. Rev. Tuberc., 60:706, 1949.
70. Zimmerman, H. A.: A study of the pulmonary circulation in man. Dis. of Chest, 20:46, 1951.

Effect of Bronchial Asthma and Chronic Pulmonary Emphysema on the Circulation

THE study of the circulation, as it is affected by the respiratory apparatus, has been greatly advanced in recent years. The cardiac catheter has made possible study of pressures and blood flow in the right heart and lesser vascular circuit.

The pulmonary vascular bed has been repeatedly shown to be a system of low resistance, the pulmonary artery pressure[4] being normally 25 mm Hg in systole and 8 mm Hg in diastole with a mean pressure of 15 mm Hg. The normal pulmonary capillary pressure[8] is 10 mm Hg, demonstrating the small gradient of only about 5 mm Hg from arteries to capillaries. In addition, the wide caliber and great distensibility of the pulmonary vascular bed is well demonstrated by the failure of moderate exercise in normal human subjects to produce an increase in pulmonary arterial pressure,[17] despite definite elevation of cardiac output.

Patients with chronic lung disease frequently have pulmonary arterial hypertension. In fact, this may sometimes be the only demonstrable evidence of altered circulation in lung disease.[5] This hypertension appears to be the outstanding point on which all investigators agree. Indeed, post-mortem studies have shown morphologic changes tending to prove that pulmonary hypertension probably existed during life. Parker,[14] for example, found at autopsy in patients with chronic pulmonary emphysema that 75 per cent had increased thickness of the right ventricle, 66 per cent had sclerosis of arterioles, and 80 per cent had sclerosis of the larger pulmonary arteries.

Evidence has been presented[3] that elevation of pulmonary artery pressure in chronic pulmonary emphysema is related to an increased vascular resistance. Hellems et al[9] have shown, and Zimmerman[20] confirmed, this to be due to pulmonary arteriolar constriction. They found, in patients with cor pulmonale, that the pulmonary capillary pressure was normal. Vasomotor effects in the pulmonary circulation have long been questioned. Much supporting evidence for such effects has now been found.

It is known that patients with pulmonary hypertension of any etiology (mitral stenosis, chronic lung disease, left ventricular failure) respond to exercise or tachycardia with a further elevation in pulmonary arterial pressure,[10,17] in contrast to normal subjects. Is this due to vasospasm or to the increased blood flow into a vascular bed of a capacity limited by congestion or anatomic changes which prevent distensibility? Certainly in patients with chronic lung disease the latter must, in part, be true. However, Motley et al[9] have shown that anoxia in normal subjects leads to elevation of pulmonary artery pressure, which may well be due to pulmonary vasoconstriction. Furthermore, widespread pulmonary vasoconstriction has been shown to result from experimental pulmonary embolism.[7,18] Zimmerman[20] adduced further supporting evidence by the fact that he could reduce pulmonary artery pressure with intravenously administered aminophylline. This drug had been previously shown to have a direct dilating effect on pulmonary arterioles in animals.

Zimmerman studied ten patients with bronchial asthma. During either spontaneous

asthma or mecholyl-induced asthma, he was able to demonstrate an average increase in pulmonary artery systolic pressure of 23.4 per cent and an average increase in diastolic pressure of 38.2 per cent. He felt that these elevated pulmonary artery pressures in an asthmatic attack were not due entirely to altered intrathoracic pressures. The mechanism suggested was that bronchial constriction and the resultant alveolar swelling transmitted pressure to the vascular bed and thereby produced increased pulmonary capillary and arteriolar pressures. Aminophylline in such cases decreased pulmonary artery pressure to levels below the normal for the patients when not in an asthmatic paroxysm. This amount of reduced pressure was believed to be caused not only by bronchodilatation but also by direct pulmonary arteriolar dilatation. Intramuscularly administered epinephrine, on the other hand, which had the same effect on the bronchi, led to a brief increase in the already elevated pulmonary artery pressure, presumably by causing pulmonary arteriolar constriction. After a few minutes, the duration of epinephrine action, the pulmonary artery pressure then did return to normal. Some of this brief further elevation in pulmonary artery pressure after epinephrine may have been due to its greater effect than aminophylline in increasing cardiac output and thus blood flow into the pulmonary vascular tree.

Even more to the point is the fact that the pulmonary hypertension of chronic cor pulmonale has been shown to be reversible.[5] Certainly anatomic changes in pulmonary vessels are not reversible, whereas physiologic changes may certainly be.

It is interesting that Borden et al[3] and Harvey et al[6] found no correlation between the degree of pulmonary hypertension and the severity of emphysema as judged by altered ratios of residual volume to total lung capacity (RV/TLC). Nor is there any correlation[6] between circulatory changes in such patients and maximum breathing capacity measurements. However, these two independent groups of investigators did find a definite and statistically highly significant correlation between the degree of arterial oxygen unsaturation and pulmonary artery pressure. This was not surprising in the light of the Cournand group's[13] other study of anoxia in normal subjects.

Patients with chronic pulmonary emphysema were then classified by Cournand and his co-workers[6] according to the degree of arterial oxygen unsaturation at rest and after a standard exercise test. Mild emphysema showed normal saturation (94-98 per cent) or only slight unsaturation (90-93 per cent) at rest and no decrease after exercise. This group of patients showed no CO_2 retention, in general, and no demonstrable circulatory alterations at rest. Severe emphysema was marked by arterial oxygen unsaturation at rest with marked unsaturation after exercise; CO_2 retention was generally present; and no evidence of heart failure was present. This group of patients had a slightly elevated resting cardiac output, pulmonary arterial hypertension, increased blood volume, and increased hematocrit readings without demonstrable change in size of pulmonary artery or of the heart.

In this connection, it was found[11] that an electrocardiographic pattern of right ventricular hypertrophy was almost always associated with a pulmonary artery mean pressure of 30 mm Hg or higher. It was also shown that the absence of a pattern associated with right ventricular hypertrophy did not rule out even marked pulmonary arterial hypertension.

Patients with chronic cor pulmonale in frank congestive failure, of course, had even greater alterations in circulation; severe arterial oxygen unsaturation (53-61 per cent), marked polycythemia and hypervolemia, severe pulmonary hypertension, high cardiac output, and marked elevation of diastolic pressure in the right ventricle. On the other hand, patients with fully compensated chronic cor pulmonale—and many of these were the same patients studied previously while in congestive failure—differed but little from the findings in the group of severe emphysema without evidence of cor pulmonale. This is a striking demonstration of reversibility in these circulatory alterations.

This work appears to explain the many observations[1,15,20] of the recent past that some patients with chronic cor pulmonale have high cardiac outputs and some low. The high cardiac output in some of these patients is explained on the basis of hypervolemia, in turn a result of chronic anoxia. Pulmonary hypertension (accentuated by the increased blood flow during the "exercise" of daily activities) and hypervolemia eventually cause right ventricular dilatation, hypertrophy and increased output, especially since such patients often have a sound myocardium. Unless they also have coronary artery disease or some other cause of myocardial deterioration, they can respond according to Starling's law of the heart, with a considerable increase in cardiac output. When the optimal stretch of the myocardial fibers have been exceeded, the cardiac output falls. It may still, however, be considerably above normal even in the presence of congestive failure. When more advanced stages of the disease processes have appeared and anoxia can no longer be relieved, myocardial deterioration leads to cardiac output values below normal. Such was the case in the final small group of patients studied. They never recovered full compensation again and died in a few months.

Anoxia, then, is believed to be the dominant abnormality in chronic pulmonary emphysema. Although some morphologic changes in the vascular bed must exist, this is less prominent in most instances, in contrast to patients with silicosis, for example. Besides, these anatomic changes are irreversible, whereas effective therapy can often correct the anoxia.

The treatment of chronic cor pulmonale in chronic pulmonary emphysema is placed on a rational basis and warrants more optimism than has been generally felt before. Anoxia must be relieved, mainly by the use of measures designed to correct bronchiolar spasm and obstruction. These have been identified[1,19] as the factors mainly responsible for the anoxia. Aerosol therapy, then, is indicated to dilate bronchioles and reduce secretions. Aminophylline, administered intravenously or rectally, should be helpful. Oxygen therapy may be used intermittently. Long continued use of oxygen in such patients may lead to narcosis[2,16] because the respiratory center, accustomed to high levels of CO_2 for some time, may rely on some degree of anoxia for its stimulus.

Antibiotics, parenterally and by the aerosol route, should be used for pulmonary infection, which may initiate acute anoxia superimposed on the chronic picture and thus produce the break in compensation.

Digitalis must be used here as in any other instance of myocardial decompensation. In acute experiments,[5] digoxin administered intravenously to patients with chronic cor pulmonale was shown to cause an increase in cardiac output and further elevation of pulmonary artery pressure (increased flow in a somewhat fixed vascular bed). However, definite reduction in the filling pressure of the right ventricle was observed, along with presumably better emptying, a reduction in the diastolic end pressure in the right ventricle.

Hypervolemia may be combatted with phlebotomies and with mercurial diuretics. In fact, one patient of Ferrer's responded to repeated venesections to the point of normal pulmonary arterial pressure. In such patients, in whom the secondary polycythemia is largely an increase in hypochromic red cells, the hematocrit is the only reliable guide to phlebotomies, for the hemoglobin may be misleading.[5]

Finally, of course, we must mention rest as a therapeutic measure which avoids accentuation of pulmonary hypertension and reduces the burden of a decompensated heart.

REFERENCES

1. Baldwin, E. de F.; Cournand, A.; and Richards, D. W., Jr.: Pulmonary insufficiency. I. Physiological classification, clinical methods of analysis, standard values in normal subjects. Medicine, 27:243, 1948.

2. Baldwin, E. de F.; Cournand, A.; and Richards, D. W., Jr.: Pulmonary insufficiency. III. A study of 122 cases of chronic pulmonary emphysema. Medicine, 28:201, 1949.
3. Borden, C. W.; Wilson, R. H.; Ebert, R. V.; and Wells, H. S.: Pulmonary hypertension in emphysema. Am. J. Med., 8:701, 1950.
4. Ellis, L. B., and Bloomfield, R. A.: Cardiac catheterization. New England J. Med., 243:339, 1950.
5. Ferrer, M. I.; Harvey, R. M.; Cathcart, R. T.; Webster, C. A.; Richards, D. W., Jr.; and Cournand, A.: Some effects of digoxin upon the heart and circulation in man: digoxin in chronic cor pulmonale. Circulation, 1:161, 1950.
6. Harvey, R. M.; Ferrer, M. I.; Richards, D. W., Jr.; and Cournand, A.: Influence of chronic pulmonary disease on the heart and circulation. Am. J. Med., 10:719, 1951.
7. Haynes, F. W.; Kinney, T. D.; Hellems, H. K.; and Dexter, L.: Circulatory changes in experimental pulmonary embolism. Federation Proc., 6:125, 1947.
8. Hellems, H. K.; Haynes, F. W.; and Dexter, L.: Pulmonary capillary pressure in man. J. Applied Physiol., 2:24, 1949.
9. Hellems, H. K.; Haynes, L. W.; Cowdey, J. S.; and Dexter, L.: Pulmonary capillary pressure in man. J. Clin. Investigation, 27:540, 1948.
10. Hickham, J. B., and Cargill, W. H.: Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. J. Clin. Investigation, 27:10, 1948.
11. Johnson, J. B.; Ferrer, M. I.; West, J. R.; and Cournand, A.: The relation between electrocardiographic evidence of right ventricular hypertrophy and pulmonary arterial pressure in patients with chronic pulmonary disease. Circulation, 1:536, 1950.
12. McMichael, J.: Circulatory failure studied by means of venous catheterization. Advances in Internal Medicine, 64. New York: Interscience Publishers, Inc., 1947.
13. Motley, H. L.; Cournand, A.; Werks, L.; Himmelstein, A.; and Dresdale, D.: Influence of short periods of induced acute anoxia upon pulmonary artery pressures in man. Am. J. Physiol., 150:315, 1947.
14. Parker, R. L.: Pulmonary emphysema. Ann. Int. Med., 14:795, 1940.
15. Richards, D. W., Jr.: Cardiac output by the catheterization technique in various clinical conditions. Federation Proc., 4:215, 1945.
16. Richards, D. W., Jr., and Barach, A. L.: The effects of oxygen treatment over long periods of time in patients with pulmonary fibrosis. Am. Rev. Tuberc., 26:253, 1932.
17. Riley, R. L.; Himmelstein, A.; Motley, H. L.; Weiner, H. M.; and Cournand, A.: Studies of pulmonary circulation at rest and during exercise in normal individuals and in patients with chronic pulmonary disease. Am. J. Physiol., 152: 372, 1948.
18. Smith, J. R., and Hara, M.: Cardiovascular dynamics in experimental embolism of restricted portions of the lungs. J. Clin. Investigation, 27:556, 1948.
19. West, J. R.; Baldwin, E. de F.; Richards, D. W., Jr., and Cournand, A.: Physiopathologic aspects of chronic pulmonary emphysema. Am. J. Med., 10:481, 1951.
20. Zimmerman, H. A.: A study of the pulmonary circulation in man. Dis. of Chest, 20:46, 1951.

Pulmonary Function Tests in Bronchial Asthma

BEFORE discussing the pulmonary function studies related to bronchial asthma, several general considerations will be discussed briefly; namely, terminology, collateral respiration, and the influence of position and of age on lung volumes.

1. *Terminology.*—For nearly a century the vital capacity stood alone as a test of pulmonary function. With the addition of new tests and more studies in recent decades, new names and many synonyms were added, leading to great confusion in terms. Therefore, a committee of respiratory physiologists recently convened and agreed upon a new terminology, which follows:[45]

Vital capacity is the maximal volume of gas that can be expelled from the lungs by forceful effort following a maximal inspiration.

Inspiratory capacity (complemental or complementary air) is the maximal volume of gas that can be inspired from the resting end-expiratory level.

Inspiratory reserve volume (complemental or complementary air, complemental air minus tidal air, inspiratory capacity minus tidal volume) is the maximal amount of gas that can be inspired from the end-inspiratory position.

Expiratory reserve volume (reserve or supplemental air) is the maximal volume of gas that can be expired from the resting end-expiratory position. In function studies the *resting* end-expiratory position is always used.

Functional residual capacity (functional residual air, sub-tidal volume, equilibrium capacity, normal capacity, mid-capacity) is the volume of gas remaining in the lungs in the resting, end-expiratory position.

Residual volume (residual capacity, residual air) is the volume of gas remaining in the lungs at the end of a maximal expiration.

Total lung capacity is the sum of vital capacity and residual volume; in other words, it is the maximal amount of gas that can be contained in the lung when it is fully expanded.

2. *Collateral Respiration.*—It had been observed that obstruction of a bronchus will result in atelectasis only if an entire lobe is obstructed. Obstruction of a bronchus beyond the second order would not, as a rule, result in atelectasis unless inflammation were present. Van Allen et al[51] investigated this problem and offered an explanation which they called "collateral respiration." Subsequent studies in experimental animals and in man by Baarsma et al,[2,3] Alley et al[1] and by Lindskog[39] corroborated the existence of ventilation between lobules not connected by bronchial passages. The evidence that follows appeared in these studies: By means of canulization of pulmonary lobules, the passage of gas to and from lobules, which are not connected by means of bronchial passages, was clearly demonstrated. The composition of the gases in such lobules remained normal, in contrast to the rapid changes in O_2 and CO_2 concentrations when an entire lobe is obstructed, which is then followed by atelectasis. In rabbits, as much as 40 per cent of the quantity of air normally supplied through bronchi reached an obstructed lobule through collateral access at a pressure difference of 2 cm water. In general, the quantity of gas sucked in collaterally proved to be directly proportionate to the negative pressure during inspiration. The existence of "vents" between lobules was also demonstrated by collateral passage of liquids and particulate matter.

Collateral respiration is maintained in man at low pressure differentials (about 1 cm water) and is easily interfered with by shallow breathing, by inflammatory reactions, and by histamine. The deleterious effect of intravenous histamine on collateral respiration was effectively blocked in animals by antihistaminic drugs.

The presence of collateral respiration probably contributes to maintaining a balance of pressure and a uniform composition of gases throughout the lung. It provides air behind a plug for effective cough, and it helps in preventing obstructive atelectasis.

3. *Influence of Position and Age on Lung Volumes.*—

(a) Position.—With a change in position of the body the lung volumina change in size. The direction of and the reasons for these changes will be obvious when we consider the changes taking place in the body when changing position.

The gravity of the abdominal viscera exert a downward pull on the diaphragm when standing upright. The greater the relaxation of the abdominal muscles, the less the opposing force to this pull. When changing to the supine position, the viscera will no longer pull the diaphragm downward, but may even push the diaphragm cephalad. Thus the chest cavity is made smaller in the supine position.

The volume of blood in the lungs is the other, even more important, influence on the size of the lung volumes. Dow[19] and Fenn et al[20] demonstrated that there is considerable displacement of blood from the chest when changing from the lying to the standing position; the changes in lung volumes were minimized by inflating cuffs about the extremities before standing up. The supine position offers a favorable condition for the accumulation of blood in the chest cavity. For twenty minutes after assuming the supine position, the cephalic end of the body will increase in weight.

All investigators measured smaller values in the lying position than in the erect position, except for the inspiratory capacity, which becomes greater.[21,29,34,42,44] The absolute values reported, of course, differ somewhat among the various groups. Kaltreider et al[34] recorded the following variations from sitting to lying position: total lung capacity—10.6 per cent; vital capacity—4.4 per cent; functional residual capacity—33.2 per cent; residual volume—27.2 per cent; expiratory reserve volume—40.7 per cent, and the inspiratory capacity + 11.2 per cent. Fowler[21] measured a decrease of 787 cc in the functional residual capacity when changing from sitting to supine position. Mills[42] reports a decrease of 300 cc in the vital capacity and Osher[44] a decrease of as much as 860 cc in the expiratory reserve volume when changing from standing to supine position.

(b) Age.—The changes with advancing age observed by Kaltreider et al,[34] Baldwin et al,[5] and others are in close agreement. All volumina decrease slightly except the residual volume and the functional residual capacity, which increase. Therefore, the residual volume to total lung capacity ratio also increases with age. Kaltreider et al[34] lists the following ratios: 19.3 per cent for the ages of 15-25 years; 20.8 per cent for 25-35 years; 23.5 per cent for 35-45 years; 23.3 per cent for 45-55 years and 30.8 per cent for the ages of 55-65 years.

LUNG VOLUMES

1. *Vital Capacity.*—The vital capacity measurement is perhaps the oldest "pulmonary function" test. It has remained in use ever since Hutchinson[32] first introduced this test in 1846. Vital capacity measurement was considered an important pulmonary function test until the early part of this century; its limitations and poor correlation with pulmonary "function" became realized, and at the same time other function tests were developed.

The vital capacity is a measurement of the difference between two *static volumes* of the lung, between that of maximum inflation and maximum deflation. In the normal person the vital capacity measurements at various times on the same person will vary but slightly. Such is not the case in patients with pulmonary disease, specifically with bronchial asthma. While the chronic asthmatic patient may have a normal vital capacity when asymptomatic, it is usually decreased during an acute asthmatic episode. Many studies have been made in recent years attempting to elicit the mechanism by which vital capacity is restricted in asthma.

Congestion of the lungs has been considered. No doubt, this is an important mechanism in decreasing vital capacity in cardiac disease. Plotz[46] demonstrated that cardiac patients with sibilant râles would increase their vital capacity by an average of 510 cc after an injection of adrenaline, while those patients with basal râles but without wheezing, did not have an increase in vital capacity. He also demonstrated an increase in vital capacity by venesection in cardiac patients as well as normal subjects. Dow[19] was able to prevent the usual increase in vital capacity which occurred when changing from lying to standing position by applying tight cuffs around all four extremities, which cut off the venous inflow to them. Sheldon and Otis[50] measured vital capacity and resistance to airflow in asthmatic subjects before and after adrenaline. The vital capacity increased in all; the alveolar pressure did not show consistent changes in either direction. Their conclusion was that adrenaline

increased the vital capacity perhaps by producing pulmonary vascular constriction rather than by bronchiolar dilatation in certain cases.

The role of bronchoconstriction has been investigated from several angles. Matheson et al[41] introduced airflow resistance experimentally in healthy young adults but was unable to alter the vital capacity appreciably. The ability of the skeletal system and lung elasticity of healthy young adults to tolerate airflow resistance during an acute experiment cannot be compared to that of the patient who perhaps has chronically increased airflow resistance. If increased airflow resistance exists, "fatigue" must sooner or later be reached and a decreased expiratory effort must follow. Not only is there, as a rule, a decreased vital capacity during clinical asthma, but there is also a prolongation and retardation of expiration, as well as an inability to return to the same initial level of expiration when performing successive vital capacities, i.e., trapping. It had been observed bronchoscopically in patients with emphysema and bronchial asthma, that the bronchial walls collapse during expiration, especially forceful expiration.[48]

In the patient with emphysema this was explained on the basis of a progressive increase in alveolar volume (loss of elasticity) without a corresponding increase in the airways leading to this volume; therefore, at the onset of expiration, when intra-alveolar pressure rises above intrabronchial pressure, the surrounding tissues become compressed, constricting the air passages more than in a normal lung during expiration; and an increase in resistance to expiratory flow results. Such mechanism would inhibit complete emptying of the lungs, or would allow complete emptying only by means of prolonged expiratory time.

It becomes clear that the vital capacity gains significance when its time relationship is considered as well. Cournand et al[13] recorded and pointed out the prolongation of expiration and improvement thereof after the use of bronchodilator aerosols. Gross[26] measured the time required for full maximal expiration in pulmonary and cardiac disease. He divided the vital capacity by the expiratory time and called this "expiratory velocity." In an effort to simplify the study of vital capacity-time relationship, Gaensler[24] used a spirometer with timing attachment. The timer can be set for one, two, or three seconds, and when the patient blows a vital capacity the volume exhaled during the first or during the first two or three seconds will be registered, as well as the total vital capacity. A simpler method is employed by Segal and Herschfus,[49] using a transparency with parallel lines. The distance between two lines corresponds to one second interval on the spirographic paper. By placing the transparency over the recorded vital capacity curve obtained on the recording kymograph tracing, the volume exhaled for each subsequent second during a single vital capacity performance can be measured. Thus it can be seen that the greatest improvement of the vital capacity by treatment is the increased volume during the first second of exhalation.

Since there is such a large variation in the size of the vital capacity between normal people, an absolute reading—e.g., 3.5 liters—will not indicate whether such vital capacity is abnormal. Many investigators have therefore tried to correlate the vital capacity with other data, and many prediction formulae have evolved. The formula of Baldwin et al[5] is generally used:

$$\text{males: } [27.63 - (0.112 \times \text{age})] \times \text{height in cm}$$
$$\text{females: } [21.78 - (0.101 \times \text{age})] \times \text{height in cm}$$

We[27] employed Baldwin's prediction formulae, but called a vital capacity of 116 per cent of predicted normal as the normal, this being the value obtained in ten normal subjects. In addition to the use of such formulae, the use of vital capacity to total lung capacity ratio has been used, the normal ratio being greater than 65 per cent.[29]

From the pulmonary function studies specifically dealing with bronchial asthma it can be concluded that the vital capacity may be normal during the asymptomatic period, but can be considerably diminished during an acute asthmatic episode. Hurtado et al[30] studied twenty-six patients, who had obstructive emphysema with "bronchitic asthma," when they were in a state of comfort. Their average vital capacity was 38.8 per cent below that predicted, and the decrease was without relation to the duration of their asthma. Subsequently, Hurtado and Kaltreider[31] studied six patients during acute bronchial asthma and found the relative as well as the absolute size of the vital capacity decreased. Epinephrine injections in five and spontaneous recovery in the sixth of these patients were followed by improvement of the vital capacity from a range of 1.60-3.40 liters to a range of 2.00-4.14 liters. One patient given epinephrine again two days after feeling well had "no appreciable changes in pulmonary capacity."

Whitfield et al[54] studied nine patients while they had obvious, moderate to severe clinical asthma. Their average vital capacity was 2.11 liters, or 39.2 per cent of the total lung capacity, and this improved after oral ephedrine to 2.53 liters, or 49.9 per cent of the total lung capacity.

In our series of patients,[27] who were studied at a time of wellbeing, the vital capacity was found to range between 51 per cent and 158 per cent of the predicted normal value. Twenty-four patients were given aminophylline, 0.5 gram i.v., and their average vital capacity rose from 3.67 liters, or 104 per cent of that predicted, to 4.03 liters, or 114 per cent of that predicted. After the use of bronchodilator aerosols, six inhalations of Neosuprel®, in twenty-nine patients, the vital capacity rose from 3.49 liters, or 102 per cent of that predicted, to 3.94 liters, or 116 per cent of that predicted.[28] Expressed in per cent of the total lung capacity, the vital capacity improved from 50.3 per cent to 54.7 per cent after aminophylline and from 53.8 per cent to 60.4 per cent after bronchodilator aerosols. Classifying our patients according to the degree of physical findings in the lungs at the time of the studies, the results were as follows: those with clear lungs gave an average vital capacity of 113 per cent of predicted normal; those with 1-plus wheezing, 102 per cent; and those with 2-plus wheezing, 95 per cent of that predicted.

2. *Inspiratory Capacity and Expiratory Reserve Volume.*—It is known that in pulmonary disease, such as emphysema, the chest is held in the so-called high inspiratory position and that such patients, of course, have a small inspiratory capacity but a relatively or absolutely large expiratory reserve volume. In 1932 Lippelt[40] had normal subjects breathe through a narrowed tube of a respirator, simulating bronchial obstruction to expiration. He observed an upward shift of the midposition, i.e., an increase in the functional residual capacity, and a simultaneous decrease in inspiratory capacity.

More recently Proctor et al[48] made the following observations during airflow studies with the pneumotachogram. If the chest wall were not opposed by lung elasticity, its resting position would be at about 70 per cent of the vital capacity. This condition is indeed seen in progressive pulmonary emphysema. Since expiration is a less forceful and more passive procedure than is inspiration, the lung volume will enlarge (i.e., emphysema) when breathing against increased resistance; the resting position of the chest shifts "upward," encroaching on the inspiratory capacity. This mechanism is seen in normal people in case of a foreign body in a bronchus and in patients with pulmonary disease giving bronchial obstruction. In patients with bronchial asthma and emphysema, alveolar pressure studies demonstrated that their resistance to expiratory airflow was higher than to inspiratory flow, instead of being equal as in normal subjects. The tendency to breathe with a larger expiratory reserve volume when faced with increased resistance, brings into play a larger elastic force during expiration.

A normal inspiratory capacity is about 75 to 80 per cent of the vital capacity; the expiratory reserve volume, the remaining 25 to 20 per cent of the vital capacity.[12] Hurtado et al[30,31] found in their patients with obstructive pulmonary emphysema and "bronchitic asthma" a mean value of 70.8 per cent for the inspiratory capacity to vital capacity ratio. In the five patients with acute bronchial asthma the inspiratory capacity to vital capacity ratio improved from a range of 54.1 per cent-80.0 per cent to a range of 60.8 per cent-86.3 per cent after epinephrine. In our study of chronic asthmatic patients during wellbeing, we, too, found the ratio of inspiratory capacity to vital capacity diminished in many patients.[27] Moreover, while the absolute values improved after treatment, the ratios changed but little. The average inspiratory capacity increased from 2.47 to 2.68 liters after i.v. aminophylline in twenty-four patients, and from 2.30 to 2.46 liters after bronchodilator aerosols in twenty-nine patients. The change in ratios was from 66 to 67 per cent, and from 64 to 65 per cent, respectively.

It appears that both the absolute and relative size of the inspiratory capacity can be improved when treating acute asthma or an acute exacerbation of chronic bronchial asthma, but that little change in ratio can be effected by further treatment of the *asymptomatic chronic asthmatic.*

3. *Functional Residual Capacity and Residual Volume.*—The various methods employed over the years in measuring the residual volume, the volume of air remaining in the lungs after a complete exhalation, have been reviewed by Comroe.[11] The closed-circuit method of Christie[10] described in 1932 has been replaced by the open-circuit method of Darling et al,[17] and Cournand et al.[16] The latter method, with various modifications, is now generally used. The method is based on gaseous nitrogen elimination from the lungs and body tissues. Pulmonary fibrosis[6] and emphysema[7] were extensively investigated with this technique by Baldwin et al.

The method of obtaining alveolar air gas samples has undergone many changes; the sample can be collected at the end of a deep expiration or at the end of normal expirations. Lambie et al[35] devised an automatic electromagnetic method for the collection of alveolar air; Bateman et al,[8] a pivoted type gasometer; or the elimination of the nitrogen can be followed by employing the continuous electronic nitrogen analyzer of Wolfe et al.[56] The open-circuit method has been standardized; the subject is allowed to breathe 100 per cent oxygen for seven minutes. The expired air is collected, measured, and analyzed, and an alveolar air sample is taken at the end of the seven minutes. The percentage of nitrogen present in that sample is called the "index of intrapulmonary mixing." The lung volume measured will be the functional residual capacity from which the residual volume and total lung capacity can be calculated. We have employed this technique in our studies.[27] Reproducibility of the functional residual capacity is limited by the sources of error in technique as well as the spontaneous variation in functional residual capacity over a period of time.[8]

Lippelt[40] demonstrated an increase in functional residual capacity and residual volume in normal subjects when breathing through narrowed tubes, simulating bronchial obstruction to expiration. Recently Whittenberger[55] explained that the increase in functional residual capacity (and total lung capacity) following obstructed breathing, as in bronchial asthma, takes place because the active phase of inspiration will inspire a larger volume of air than the less forceful phase of expiration will be able to expire. As the volume increases and the lung stretches, the lung will acquire additional energy and expel a larger tidal volume; equilibrium is reached until there is further loss of elasticity, followed by further increase in lung volume. The enlarged functional residual capacity causes a drop in pO_2 and necessitates increased ventilation to maintain adequate CO_2 elimination.

The relative size of the residual volume is usually expressed as the per cent of

the total lung capacity. In normal people this residual volume/total lung capacity ratio is less than 30 per cent; a ratio greater than 35 per cent is definitely abnormal.[14,29]

In acute asthma both the functional residual capacity and residual volume are considerably enlarged. After an injection of epinephrine, Hurtado and Kaltreider[31] found that the residual volume improved and "approached" normal values. In the patients treated with oral ephedrine, Whitfield et al[54] measured a change in the residual volume/total lung capacity ratio from 60.8 per cent to 50.1 per cent. Baldwin[4] reported a normal residual volume and residual volume/total lung capacity ratio in asthmatic patients during an asthma-free period. We studied thirty-five patients at a time of relative or complete comfort from bronchial asthma.[27] The fifty-three determinations of residual volume/total lung capacity ratio on these patients ranged between 35 per cent and 57 per cent with an average value of 47.0 per cent. There was insignificant improvement of this ratio after treatment with either aminophylline or bronchodilator aerosols.

4. *Total Lung Capacity and Residual Volume to Total Lung Capacity Ratio.*—The same mechanisms which lead to an enlarged functional residual capacity in bronchial asthma are responsible for the simultaneous enlargement of the total lung capacity (see above). The measurement of the total lung capacity depends on measuring the functional residual capacity as described before. The functional residual capacity plus the inspiratory capacity constitute the total lung capacity.

To evaluate the absolute size of a given total lung capacity as being normal or abnormal requires a way of predicting the normal total lung capacity for that particular individual. However, Fowler and Comroe[11,12] state that at best the normal total lung capacity cannot be predicted closer than 15 to 20 per cent. The most common formula for predicting total lung capacity is based on the ratio of vital capacity to total lung capacity, which varies with age. The formula is $\frac{VC}{A}$ where $A = 80$ for the ages of 16-34 years; $A = 76.6$ for 35-49 years; and $A = 69.2$ for 50-69 years.[34] However, in pulmonary disease, and especially bronchial asthma, the vital capacity varies greatly and is usually low. Therefore, calculating the total lung capacity with such vital capacities would yield abnormally low so-called "normal" predicted total lung capacities and, moreover, they would vary tremendously from one time to another. For this reason other investigators used the predicted vital capacity to calculate the predicted total lung capacity.[56] However, we have pointed out that the prediction formula for vital capacity usually yields a too small vital capacity in normal subjects and very often in asthmatic patients when they feel well. Therefore, using the predicted vital capacity yields a predicted total lung capacity which usually is too small. In order to eliminate both of the above objections in calculating the normal total lung capacity, we have used the largest actually obtained vital capacity, either before or after treatment, of the asthmatic subject. Only if the vital capacity, even after treatment, would be less than the value calculated with the prediction formula would the predicted vital capacity be used in predicting the total lung capacity. Bateman[8] has recently shown that the best correlation of the total lung capacity is with body height.

Hurtado et al[30] found the total lung capacity 5.7 per cent below predicted in their twenty-six patients with obstructive emphysema and "bronchitic asthma" (range between 3.82 liters to 8.54 liters). In five patients with acute asthma these authors found a marked decrease in total lung capacity after treatment with epinephrine.[31] Before treatment the total lung capacity ranged between 4.74 liters and 10.02 liters; after treatment, between 3.94 liters and 6.91 liters. Whitfield et al[54] did not find a significant reduction in total lung capacity when he treated nine patients, with emphy-

sema and obvious clinical asthma, with oral ephedrine. Baldwin[4] found a normal total lung capacity in ten patients studied during an asthma-free period, and an increase of the total lung capacity by 900 cc when one of these patients developed acute asthma.

Our fifty-three determinations on thirty-five patients yielded an average total lung capacity of 6.92 liters, or 125 per cent of predicted normal.[27] The prediction formula applied to normal subjects gave a total lung capacity of 120 per cent of predicted. We found that 60 per cent of asthmatic patients had a total lung capacity greater than normal (i.e., greater than 120 per cent of predicted) even when in a state of wellbeing. Treatment with either i.v. aminophylline or bronchodilator aerosols resulted in a slight and insignificant increase in the average value of total lung capacity; 0.8 per cent and 0.4 per cent increase, respectively. We are studying several asthmatic patients with remissions of eight months or longer. Even in these cases we find the total lung capacity larger than the predicted normal value.

Since the absolute values of either residual volume or total lung capacity do not indicate normalcy, and since the residual volume bears a definite relationship to the total lung capacity, varying somewhat with age, this ratio of residual volume/total lung capacity x 100 is of great significance in the study of pulmonary disease. The normal values for this ratio are 20.0 per cent for 16-34 years, 23.4 per cent for 35-49 years, and 30.8 per cent for 50-69 years. Not only is an increased ratio considered to be about the best indicator of the presence of emphysema, but also of the degree and severity.[30] According to Baldwin et al, the severity of emphysema should be judged by the status of the arterial blood gases.

An elevated residual volume/total lung capacity ratio is seen in patients with acute asthma. During an asthma-free period, Baldwin[4] found a normal ratio. In our group of patients this ratio was elevated even though many were completely symptom-free.[27] While Hurtado et al[30] did not find a relationship between the number of years of bronchitic asthma and pulmonary capacity abnormality, we found a fairly good relationship.[27] Irrespective of age, the residual volume/total lung capacity ratio ranged between 35 and 67 per cent in our thirty-five patients. After i.v. aminophylline the average improvement was 7.4 per cent, and after bronchodilator aerosols, 8.1 per cent.

VENTILATION STUDIES

Lung volumes as discussed above are essentially static measurements. Pulmonary ventilation, however, relates to the movement of air in and out of the lungs and is evaluated as a volume-time measurement. Under physiologic conditions, pulmonary ventilation varies from minimal values during rest and sleep to maximal values during exhausting exercise. The former is measured as the *resting minute ventilation*, the latter as the *maximum breathing capacity;* and the difference between these two is the *ventilatory reserve.*

1. *Minute Ventilation.*—An increase of resting ventilation is commonly observed in patients with pulmonary fibrosis or obstructive emphysema.[33] The mechanism for this altered function is not well understood. Partial, mild airway obstruction may give either an increase or decrease in respiratory minute volume, but severe obstruction usually is followed by a decrease.[55] It has also been demonstrated that an increase in oxygen in the inspired air will give hypoventilation, and a decrease in oxygen will give hyperventilation. Hyperventilation results in a decrease of the aeration gradient which was found by Motley et al[43] to be elevated in many patients with pulmonary fibrosis and emphysema. In other words, resting *ventilation* increases in order to maintain adequate resting *respiratory* function. The minute ventilation is increased above normal levels in such patients during exercise also. The maximum breathing capacity, on the other hand, as will be described, is the limit of ventilation in normal people as well as in patients.

The average normal value for resting minute ventilation per sq m body surface is given at 3.6 liters for males and 3.2 liters for females.[12]

Baldwin[4] observed hyperventilation during rest, one minute exercise, and first minute of recovery in ten asymptomatic patients. These patients had a normal residual volume and residual volume/total lung capacity ratio. The resting ventilation in thirty-two of our patients studied averaged 5.42 liters per sq m.[27] After treatment with either intravenous aminophylline or bronchodilator aerosols the resting ventilation increased further in most patients.

2. *Maximum Breathing Capacity.*—A very important ventilation factor which limits the extent of physical exertion is the maximum breathing capacity (MBC). This capacity depends secondarily on many other factors, such as the size of the pulmonary bellows, the muscular force available, and the resistance to airflow.[41] Matheson et al[41] observed marked reduction of ventilation capacity (MBC) by experimental increase in airflow resistance, while the vital capacity remained unaffected. Performance of maximum breathing capacity depends on the ability to develop high flow velocities. Proctor et al[18] demonstrated that patients with pulmonary diseases are unable to produce high flow velocities; the pathologic changes of the bronchial tree are such as to cause turbulence at velocities of only 20-30 liters/minute; increased tissue viscosity of the lungs as well as decreased elasticity also interferes with the development of high flow velocities.

The maximum breathing capacity varies a great deal between normal individuals, as is seen with every other pulmonary test. In order to evaluate a given maximum breathing capacity, factors of correlation have been used and several prediction formulae have been developed. Gray et al[25] found no relationship between the maximum breathing capacity and age, height, or weight, and only slight relationship to body surface. They measured the maximum breathing capacity in a large number of healthy young individuals and found the following normal values: 167.1 liters/minute + 13 per cent for males and 115.8 liters/minute + 18 per cent for females. In these studies the maximum breathing capacity was performed for 20 seconds. We[27] used the prediction formulae of Baldwin, and we had our patients perform the maximum breathing capacity for twelve seconds only, since this is the limit of tolerance for asthmatic subjects without precipitating acute asthma.

Baldwin[4] found the maximum breathing capacity markedly decreased in nine of the ten patients studied during an asthma-free period; the mean value was 58 per cent of predicted, and this increased to 81 per cent after bronchodilator aerosols.

We[27] found in a group of twenty-two asymptomatic patients an average maximum breathing capacity of 65.2 per cent of predicted normal, which increased to 82.3 per cent after intravenous aminophylline; a 31 per cent improvement. After bronchodilator aerosols in twenty-eight patients the average maximum breathing capacity increased from 62.6 per cent to 85.7 per cent of predicted normal, a 50 per cent improvement. Classifying the patients according to the chest findings, the average values were 75.0 per cent of the predicted normal for those with clear lungs, 51.8 per cent for those with 1-plus wheezing, and 46.6 per cent for those with 2-plus wheezing.

3. *Ventilatory Reserve and Walking Index.*—An increase in physical activity requires an increase of ventilation above resting ventilation values. The extent of impairment of the ventilatory function will be expressed by the ventilation reserve, which is the difference between resting ventilation and maximum breathing capacity. A decrease in ventilatory reserve will result either from an increased resting ventilation, in order to maintain adequate resting respiratory function, or from a decreased maximum breathing capacity, secondary to many factors described above.

Increased pulmonary ventilation (hyperpnea) can be of two types: 1. metabolic hyperpnea, where the increased pulmonary ventilation follows an increased metabol-

ism; e.g., exercise, hyperthyroidism; and 2. compensatory hyperpnea, where the increased pulmonary ventilation is out of proportion to the metabolism. The latter type is seen in pulmonary disease. The difference between these two types is determined by the *ventilation equivalent,* which is the liters of ventilation per 100 cc of oxygen consumed. This equivalent is normal in metabolic hyperpnea, but increased in compensatory hyperpnea.

A common way of expressing the ventilatory reserve is by the formula:

$$\frac{\text{MBC—Minute ventilation}}{\text{MBC}} \times 100$$

The reserve will be greater than 95 per cent in normal people; when less than 70 per cent, severe exertional dyspnea exists.[45]

In our[27] asthmatic patients, we measured a decreased maximum breathing capacity and an increased resting ventilation in all but a few; in other words, ***most patients with chronic bronchial asthma have a diminished ventilatory reserve even when in a state of comfort.***

Others[52,53] have used the walking ventilation test to measure ventilatory function. The patient walks on level ground, 180 feet per minute for three minutes. The average normal value is between 12 and 19 liters per minute. Warring[52] used the ratio of walking ventilation to maximum breathing capacity; this he called the "walking index." He found a definite relationship between the walking index to the degree of dyspnea. When the index is approximately 0.35, slight dyspnea is present; moderate dyspnea at 0.45 and severe exertional dyspnea will be present when the index is higher than 0.50.

4. *Air Velocity Index.*—In order to obtain valuable information from two simple tests, Gaensler[23] compared the vital capacity and the maximum breathing capacity. The former test is a measure of volume but does not reveal partial obstruction of the bronchial passages or decrease of lung elasticity. The MBC, however, will be low with such pulmonary pathology as well as with a decrease in available ventilating lung tissue. By using the ratio of per cent of predicted maximum breathing capacity over the per cent of predicted vital capacity, the resulting "Air Velocity Index" (AVI) will indicate whether there is more obstruction to airflow than there is loss of lung tissue or vice versa. Thus, in patients with bronchial asthma, the air velocity index will be much less than 1.0 (ranging between 0.19 and 0.88), while in patients with loss of aerated lung tissue the air velocity index will be greater than 1.0. The index should not be interpreted without the absolute values from which it is derived, since a proportionate decrease in both maximum breathing capacity and vital capacity will result in a normal index of 1.0.

5. *Intrapulmonary Gas Mixing.*—Proper pulmonary ventilation depends on even distribution of the effective tidal air to the actively perfused alveoli. The effective tidal air is the volume of the breath taken minus the respiratory dead space, or volume of the tracheobronchial passages. The respiratory dead space measures approximately 150 to 200 cc.[22] The average value of the normal effective tidal volume is approximately 350 cc, and this amount diffuses into and mixes with the pulmonary residual volume. Under normal circumstances the effective tidal air diffuses readily and equal aeration of the alveoli takes place. When the residual volume is large, or when alveoli communicate through partially obstructed passages, ventilation will be poor in such areas. The effectiveness of pulmonary aeration is reflected by the pulmonary emptying rate, and the completeness thereof is expressed by the "index of intrapulmonary mixing"[14,17,18] (index). The index indicates the completeness of removal of nitrogen from the alveoli after breathing 100 per cent oxygen for a period of seven minutes. The normal index is less than 2.5 per cent nitrogen.[14]

The index will, as a rule, be found to be abnormal in patients with emphysema, bronchial asthma, bronchiectasis, congestive heart failure, et cetera; yet, at times a normal value may be obtained in the presence of pulmonary disease with unequal alveolar aeration. The index depends on the total lung capacity, the effective tidal volume, the respiratory rate, and the distribution factor.[12] Measuring the alveolar nitrogen at the end of seven minutes of breathing 100 per cent oxygen, according to the conventional method of Darling et al,[16,17,18] does not take into account such variables. Wolfe et al[56] studied the mixing index with an electronic nitrogen analyzer, giving continuous readings and taking into consideration the variable factors. Indeed, they found abnormal emptying rates with a normal end reading after seven minutes accomplished by hyperventilation.

The significance of effective alveolar aeration is, of course, its function in respiratory gas exchange. Motley et al,[43] studying oxygen transport in the lungs in pulmonary fibrosis and emphysema, found increased alveolar-arterial oxygen gradients in 60 per cent of such patients. On the basis of their studies with high and low oxygen mixtures and with intermittent positive pressure breathing, these investigators demonstrated that improved and uniform alveolar aeration was followed by a lowering of the aeration gradient and vice versa. Poor alveolar aeration will result in a lowered pO_2 in such alveoli, followed by arterial blood unsaturation, since the blood can take on oxygen only in proportion to the partial pressure in the respective alveoli.

Even though the index may be high, such patients do not necessarily show arterial hypoxia. Investigations have demonstrated an effective mechanism for shunting blood away from unaerated to aerated sections of the lungs, thus maintaining adequate arterial oxygenation despite the presence of poorly ventilated alveoli.[15]

Baldwin[4] found a mean value of 4.5 per cent nitrogen for index among ten asthmatic patients during an asthma-free period. The index was above 2.5 per cent in all patients, even though they all had normal lung volumes and normal residual volume/total lung capacity ratios. All these patients hyperventilated at rest. Among our thirty-five asthmatic patients,[27] the index ranged between 1.0 per cent and 12.12 per cent nitrogen, and averaged 4.05 per cent nitrogen. The influence of efficiency of ventilation on the index is demonstrated by the following: 1. The patients with clear lungs on physical examination had an average index of 3.26 per cent nitrogen, those with 1-plus wheezing had 3.95 per cent, and those with 2-plus wheezing had 5.43 per cent nitrogen. 2. After treatment with intravenous aminophylline the index showed an improvement of 32.7 per cent and averaged 2.22 per cent nitrogen; after bronchodilator aerosols the average improvement was 28.8 per cent, and the index was improved to an average value of 2.97 per cent nitrogen.[27]

6. *Instantaneous Air Flow Measurements.*—

(a) *Maximum Expiratory Velocity (MEV).*—We[27] have described the use of a simple, inexpensive apparatus which measures the instantaneous maximum expiratory air flow, called maximum expiratory velocity (MEV). The combination of this test with the vital capacity will give information similar to that obtained from the vital capacity and maximum breathing capacity.

The ability of giving a high MEV reading depends on the production of a high flow velocity of air. Factors affecting or interfering with high air velocity were discussed before. Proctor et al[48] studied peak flows during a maximum expiratory puff (equivalent to our MEV) and during maximum inspiration. They measured normal peak flows of 300 to 400 liters/minute reached in 0.1 second during expiration, and slightly lower values reached in 0.23 seconds during inspiration.

In fifty normal subjects the MEV was greater than 7.5 liters per second.[27] The average value obtained from thirty-one asthmatic subjects was 3.9 liters per second; only four out of forty-one determinations were 7.5 liters per second or higher. After

intravenous aminophylline, the MEV improved 30.6 per cent and after bronchodilator aerosols it improved 58.5 per cent.[27]

(b) *Pneumotachograph.*—The development of the pneumotachograph by Lee and Silverman[36] in 1943 has opened many new avenues in the study of pulmonary ventilation. At first it was an instrument which measured instantaneous rate of air flow during inspiration; subsequently, an instrument was designed to study expiratory air flow.[37] Since then, the instrument has undergone changes and improvements to give instantaneous response in both inspiration and expiration with minimal lag and inertia, and without significant resistance to air flow. With such an apparatus detailed studies on air flow and factors governing air flow have been reported by Silverman,[38] Proctor et al[47,48] and others. Normal subjects and those with pulmonary disease have been studied extensively; the effects of age, posture, resistance, et cetera, have all been subjects of investigation.

When a normal subject breathed through expiratory resistance produced experimentally, the following changes were observed from the normal pneumotachogram:[38]

1. The inspiratory curve showed an increase in amplitude and a decrease in the inspiratory phase in per cent of the total respiratory cycle.

2. The expiratory curve was damped, the rise to maximum flow was delayed, and there was a sudden change in flow at the end of the cycle instead of a smooth gradual return to the zero line. Similar curves were obtained with the pneumotachograph when studying asthmatic subjects. Patients with primary pulmonary emphysema showed curves which were almost rectangular, were considerably damped, and had a rapid return to zero.

With this apparatus, peak flows of a single maximum expiratory effort and inspiratory effort have been measured, and the effects of increased expiratory resistance on air flow velocities have been recorded in normal subjects and in subjects with pulmonary disease.[36,37,38,48] These data are discussed in previous chapters.

REFERENCES

1. Alley, R. D., and Lindskog, G. E.: Pharmacologic factors influencing collateral respiration; possible relation to the etiology of pulmonary complications. Ann. Surgery, 128:497, 1948.
2. Baarsma, P. R., and Dirken, M. N. J.: Collateral ventilation. J. Thoracic Surg., 17:238, 1948.
3. Baarsma, P. R.; Dirken, M. N. J.; and Huizinga, E.: Collateral ventilation in man. J. Thoracic Surg., 17:252, 1948.
4. Baldwin, E.: Bronchial asthma. Am. J. Med., 1:189, 1946.
5. Baldwin, E.; Cournand, A.; and Richards, D. W., Jr.: Pulmonary insufficiency. I. Physiological classification, Clinical methods of analysis, Standard values in normal subjects. Medicine, 27:243, 1948.
6. Baldwin, E.; Cournand, A.; and Richards, D. W., Jr.: Pulmonary insufficiency. II. A study of thirty-nine cases of pulmonary fibrosis. Medicine, 28:1, 1949.
7. Baldwin, E.; Cournand, A.; and Richards, D. W., Jr.: Pulmonary insufficiency. III. A study of 122 cases of chronic pulmonary emphysema. Medicine, 28:201, 1949.
8. Bateman, J. B.: Studies of lung capacities and intrapulmonary mixing; normal lung capacities. J. Appl. Physiol., 3:133, 1950.
9. Bateman, J. B.; Boothby, W. M.; and Helmholz, H. F., Jr.: Studies of lung volumes and intrapulmonary mixing; notes on open circuit methods, including use of a new pivoted type gasometer for lung clearance studies. J. Clin. Investigation, 28:679, 1949.
10. Christie, R.: The lung volume and its subdivisions. I. Methods of measurement. J. Clin. Investigation, 11:1099, 1932.
11. Comroe, J. H., Jr., Ed.-in-Chief: Methods in Medical Research. Chicago: Year Book Publishers, Inc., 2:181, 1950.

12. Comroe, J. H., Jr.: Interpretation of commonly used pulmonary function tests. Am. J. Med., 10:356, 1951.
13. Cournand, A.; Richards, D. W., Jr.; and Darling, R. C.: Graphic tracings of respiration in study of pulmonary disease. Am. Rev. Tuberc., 40:487, 1939.
14. Cournand, A.; Baldwin, E.; Darling, R. C.; and Richards, D. W., Jr.: Studies of intrapulmonary mixture of gases. IV. The significance of the pulmonary emptying rate and simplified open circuit measurement of residual air. J. Clin. Investigation, 20:681, 1941.
15. Cournand, A.: Recent observations on the dynamics of the pulmonary circulation. Bull. New York Acad. Med., 23:27, 1947.
16. Cournand, A.; Riley, R. L.; and Yarmuth, I. G.: Influence of body size on gaseous nitrogen elimination during high oxygen breathing. Proc. Soc. Exper. Biol. & Med., 48:280, 1941.
17. Darling, R. C.; Cournand, A.; Mansfield, J. S.; and Richards, D. W., Jr.: Studies on intrapulmonary mixture of gases: Nitrogen elimination from blood and body tissues during high O_2 breathing. J. Clin. Investigation, 19:591, 1940.
18. Darling, R. C.; Cournand, A.; and Richards, D. W., Jr.: Studies on intrapulmonary mixture of gases: an open circuit method for measuring residual air. J. Clin. Investigation, 19:609, 1940.
19. Dow, P.: The venous return as a factor affecting the vital capacity. Am. J. Physiol., 127:793, 1939.
20. Fenn, W. O.; Otis, A. B.; Rahn, H.; Chadwick, L. E.; and Hegnauer, A.: Displacement of blood from the lungs by pressure breathing. Am. J. Physiol., 151:258, 1947.
21. Fowler, W. S.: Lung function studies. IV. Postural changes in respiratory dead space and functional residual capacity. J. Clin. Investigation, 29:1437, 1950.
22. Fowler, W. S.: Lung function studies. V. Respiratory dead space in old age and in pulmonary emphysema. J. Clin. Investigation, 29:1439, 1950.
23. Gaensler, E. A.: Ventilatory tests in bronchial asthma. J. Allergy, 21:232, 1950.
24. Gaensler, E. A.: Analysis of the ventilatory defect by timed capacity measurements. Am. Rev. Tuberc., 64:256, 1951.
25. Gray, J. S.; Barnum, D. R.; Matheson, H. W.; and Spies, S. N.: Ventilatory function tests. I. Voluntary ventilation capacity. J. Clin. Investigation, 29:677, 1950.
26. Gross, D.: Investigations concerning vital capacity. Am. Heart J., 25:335, 1943.
27. Herschfus, J. A.; Bresnick, E.; and Segal, M. S.: Pulmonary function studies in bronchial asthma. I. In the control state. II. After treatment. In press.
28. Herschfus, J. A.; Bresnick, E.; Levinson, L.; and Segal, M. S.: A new sympathomimetic amine (Neosuprel) in the treatment of bronchial asthma. Ann. Allergy, 9:769-773 (Nov.-Dec.) 1951.
29. Hurtado, A., and Boller, C.: Studies of total pulmonary capacity and its subdivisions. I. Normal, absolute and relative values. J. Clin. Investigation, 12:793, 1933.
30. Hurtado, A ; Kaltreider, N. L.; Fray, W. W.; Brooks, W. D. W.; and McCann, W. S.: Studies of total pulmonary capacity and its subdivisions. VI. Observations on cases of obstructive pulmonary emphysema. J. Clin. Investigation, 13:1027, 1934.
31. Hurtado, A., and Kaltreider, N. L.: Studies of total pulmonary capacity and its subdivisions. VII. Observations during the acute respiratory distress of bronchial asthma and following the administration of epinephrine. J. Clin. Investigation, 13:1053, 1934.
32. Hutchinson, J.: On the capacity of the lungs and on the respiratory functions, with a view of establishing a precise and easy method of detecting disease by the spirometer. Tr. Med. Chir. Soc. London, 29:137, 1846.
33. Kaltreider, N. L., and McCann, W. S.: Respiratory response during exercise in pulmonary fibrosis and emphysema. J. Clin. Investigation, 16:23, 1937.
34. Kaltreider, N. L.; Fray, W. W.; and Van Zile Hyde, H.: The effect of age on the total pulmonary capacity and its subdivisions. Am. Rev. Tuberc., 37:662, 1938.
35. Lambie, C. G., and Morrissey, M. J.: An automatic method for the collection of the alveolar air. J. Physiol., 107:14, 1948.
36. Lee, R. C., and Silverman, L.: An apparatus for measuring airflow during inspiration. Rev. Sci. Instruments, 14:174, 1943.

37. Silverman, L.; Lee, R. C.; and Drinker, C. K.: A new method for studying breathing, with observations upon normal and abnormal subjects. J. Clin. Investigation, 23:907, 1944.
38. Silverman, L.: Respiratory air flow characteristics and their relation to certain lung conditions occurring in industry. J. Indust. Hyg. & Toxicol., 28:183, 1946.
39. Lindskog, G. E.: Collateral respiration in the normal and diseased lung. Yale J. Biol. and Med., 23:311, 1951.
40. Lippelt, H.: Einfluss der stenosenatmung auf lunger ventilation und lungervolumina bein gesunden. Beitr. z Klin. Tuberk., 81:520, 1932.
41. Matheson, H. W.; Spies, S. N.; Gray, J. S.; and Barnum, D. R.: Ventilatory function tests. II. Factors affecting the voluntary ventilation capacity. J. Clin. Investigation, 29:682, 1950.
42. Mills, J. N.: The influence upon the vital capacity of procedures calculated to alter the volume of blood in the lungs. J. Physiol., 110:207, 1949.
43. Motley, H. R., and Tomashefski, J. F.: Effect of high and low oxygen levels and intermittent positive pressure breathing on oxygen transport in the lungs in pulmonary fibrosis and emphysema. J. Appl. Physiol., 3:189, 1950.
44. Osher, W. J.: Change of vital capacity with the assumption of the supine position. Am. J. Physiol., 161:352, 1950.
45. Pappenheimer, J. R.: Standardization of definitions and symbols in respiratory physiology. Federation Proc., 9:602, 1950.
46. Plotz, M.: Bronchial spasm in cardiac asthma. Ann. Int. Med., 26:521, 1947.
47. Proctor, D. E., and Hardy, J. B.: Studies of respiratory air flow. I. Significance of the normal pneumotachogram. Bull. Johns Hopkins Hosp., 85:253, 1949.
48. Proctor, D. E.; Hardy, J. B.; and McLean, R.: Studies of respiratory air flow. II. Observations on patients with pulmonary disease. Bull. Johns Hopkins Hosp., 87:225, 1950.
49. Segal, M. S., and Herschfus, J. A.: A simple method for the determination of vital capacity-time relationships. In press.
50. Sheldon, M. B., and Otis, A. B.: Effect of adrenalin on resistance to gas flow in the respiratory tract and on the vital capacity of normal and asthmatic subjects. J. Appl. Physiol., 3:513, 1951.
51. Van Allen, C. M.; Lindskog, G. E.; and Richter, H. G.: Gaseous interchange between adiacent lung lobules. Yale J. Biol. & Med., 2:297, 1930.
52. Warring, F. C., Jr.: Ventilatory function. Experiences with a simple practical procedure for its evaluation in patients with pulmonary tuberculosis. Am. Rev. Tuberc., 51:432, 1945.
53. Warring, F. C., Jr.: Simple tests of ventilatory function for use in the sanatorium or clinic. Am. Rev. Tuberc., 60:149, 1949.
54. Whitfield, A. G. W.; Arnott, W. M.; and Waterhouse, J. A. H.: The effect of ephedrine in asthma and emphysema. Quart. J. Med., 19:319, 1950.
55. Whittenberger, J. L.: Lung volume and air flow characteristics in asthma. Treatment of Asthma. H. A. Abramson, M.D., Ed. Baltimore: Williams & Wilkins Co., 1951.
56. Wolfe, W. A., and Carlson, L. D.: Studies of pulmonary capacity and mixing with the nitrogen meter. J. Clin. Investigation, 29:1568, 1950.

EDITORIAL

(Continued from Page 779)

Sharp and Dohme, convinced of the necessity of placing so highly desirable a therapeutic weapon in the hands of every practicing physician, has resumed the manufacture of the bovine type of tetanus antitoxin, although it will never be a commercially profitable venture. For the patients who will be saved needless worry, and perhaps suffering, and for the physicians who will be saved much concern, this editorial will, it is hoped, give the company and its product the widest possible publicity. The people at Sharp and Dohme responsible for this outstanding example of public service and good will deserve the highest commendation.

News Items

INTERNATIONAL ASSOCIATION OF ALLERGOLOGY
(International Association of Allergists)

The International Association of Allergists held its First Congress at Zurich, Switzerland, September 23-29, 1951. This was followed by a symposium on the influence of the hypophysis and the adrenal cortex on biological reactions arranged by the Swiss Academy of Medical Sciences, October 1 and 2. The approximate registration was 600, representing officially twenty-eight allergy societies from all over the world. The Congress was held under the high patronage of the Swiss Federal Council, and the honorary president was Dr. Ph. Etter, Head of the Department of the Interior. There were nineteen scientists of Switzerland representing the honorary committee. The committee of organization consisted of Prof. Dr. Ch. W. Loeffler, President; Prof. Dr. A. S. Grumbach, General Secretary; and Dir. A. G. Mann, Treasurer.

Dr. A. R. Rich, of Baltimore, was a guest speaker at the Congress. Over 200 papers were presented covering all phases of the subject of allergy and the fundamental sciences pertaining to allergy.

A permanent committee on nomenclature and one on constitution and by-laws were appointed, and a new constitution and by-laws was adopted. The name of the society has been changed to The International Society of Allergology. The following officers were elected for four years:

President: Fred W. Wittich, U.S.A.
President-Elect: Samuel M. Feinberg, U.S.A.
First Vice President: Ulysses Fabiano Alves, Jr., Brazil
Second Vice President: Pasteur Vallery-Radot, France
Third Vice President: David A. Williams, England
Secretary-General: Bernard N. Halpern, France
Treasurer: Arthur S. Grumbach, Switzerland.

The Executive Committee is comprised of the above officers together with four members-at-large: Charles W. Loeffler, Switzerland; Egon Bruun, Denmark; Ethan Allan Brown, U.S.A.; Francis M. Rackemann, U.S.A.; and Mario Salazar-Mallen, Mexico.

The next meeting will be held in the early fall of 1955 at Rio de Janeiro, Brazil.

NEW SECTION ON ALLERGY

A Section on Allergy has been organized in the Medical Society of the County of Kings and Academy of Medicine of Brooklyn. The following officers and members of the Executive Council were elected by the Founder Members at their first meeting on October 23, 1951:

President: George Adams Merrill, M.D.
Vice President: Emanuel Schwartz, M.D., F.A.C.A.
Secretary-Treasurer: Harry Leibowitz, M.D., F.A.C.A.
Executive Council: Harry Markow, M.D., F.A.C.A.; Richard H. Bennett, M.D.; Solomon Slepian, M.D., F.A.C.A.; William Messer, M.D., F.A.C.A.; Arthur William Grace, M.D.; Charles Spratt, M.D., F.A.C.A., and Clifford DeRago, M.D.

The first scientific meeting was held on Tuesday, November 13, 1951, in the Kings County Medical Society Building. Speaker was Dr. Louis Tuft, Associate Professor of Medicine, Chief of Clinic of Allergy and Applied Immunology, Temple University

Hospital, Philadelphia, his subject being "Allergy Problems in General Practice and Their Management."

Address of the Section on Allergy is 1313 Bedford Avenue, Brooklyn 16, New York.

PENNSYLVANIA ALLERGY ASSOCIATION

At the fall meeting of the Pennsylvania Allergy Association at Geisinger Hospital, Danville, Pennsylvania, the following officers were elected for 1951-52:

President: John Foster, Jr., M.D., Harrisburg

Vice President: Luther King, M.D., Meadville

Secretary-Treasurer: Ralph Mulligan, M.D., F.A.C.A., Reading

Board of Regents: Jean Crump, M.D., Philadelphia; and Stephen Lockey, M.D., F.A.C.A., Lancaster

The following were elected to membership: Dr. Stanley Sutula, Wilkes-Barre; Dr. Leo Hellman, Port Allegheny; Dr. Louis Tuft, Philadelphia; Dr. Robert Allen, Reading; and Dr. Donald Walker (Associate, ACA), Sharon.

Dr. Ralph Mulligan, of Reading, reported that an allergy campaign in Berks County netted $5,136. Of the 20 per cent of this amount that goes to the state organization to be used for research work, $500 has already been apportioned to Dr. Lester P. Fowle and Prof. J. W. Rice, Ph.D., of Bucknell University for research work in eczema. The 80 per cent remains in Berks County for educational guidance and clinic work in the three Reading hospitals.

The three-day spring meeting of the Association will be held at Galen Hall, May 17, 18, and 19.

ALLERGY SECTION MEETING, AMERICAN ACADEMY OF PEDIATRICS

An Allergy Section was held at the twentieth annual meeting of the American Academy of Pediatrics in Toronto, Ontario, Canada, October 21. A Panel on Endocrine Therapy in Pediatric Allergy, Thyroid, ACTH and Cortisone was moderated by Bret Ratner, M.D., F.A.C.A. Topics discussed were "Basic Physiological Changes Induced by Thyroid, ACTH and Cortisone" by Joseph A. Johnston, M.D., Detroit; "Hypothyroidism in Children" by William A. Reilly, M.D., Little Rock, Arkansas; "Bone Maturation and Capillary Microscopy as Indicators for the Use of Thyroid" by Bret Ratner, M.D., F.A.C.A., New York City; "ACTH and Cortisone Therapy in Urticaria" by Harry L. Bacal, M.D., Montreal; "ACTH and Cortisone Therapy in Hay Fever" by Harold E. Edwards, M.D., Toronto; "ACTH and Cortisone Therapy in Eczema" by Jerome Glaser, M.D., F.A.C.A., Rochester, N. Y.; and "ACTH and Cortisone Therapy in Asthma" by James C. Overall, M.D., Nashville.

CHICAGO SOCIETY OF ALLERGY

The following are the newly elected officers of the Chicago Society of Allergy for 1951-52:

President: Theron G. Randolph, M.D., F.A.C.A.

President-Elect: Milton M. Mosko, M.D.

Secretary-Treasurer: Abe L. Aaronson, M.D., F.A.C.A.

Program Chairman: Morris A. Kaplan, M.D., F.A.C.A.

Public Relations Committee: Leon Unger, M.D., F.A.C.A., and Michael Zeller, M.D., F.A.C.A.

MICHIGAN ALLERGY SOCETY

At the last meeting of the Michigan Allergy Society these officers were elected:

President: Homer A. Howes, M.D., Detroit

Vice President: Jack Rom, M.D., F.A.C.A., Detroit

Secretary-Treasurer: Frank F. A. Rawling, M.D., Toledo, Ohio.

The Executive Committee is comprised of the foregoing officers plus Meryl M. Fenton, M.D., F.A.C.A.; Sidney Friedlaender, M.D., F.A.C.A.; and Donald S. Smith, M.D.

ALLERGY SECTION, SOUTHERN MEDICAL ASSOCIATION

The allergy Section of the Southern Medical Association convened on November 5 and 6 in Dallas, Texas. Alan Cazort, M.D., F.A.C.A., opened the program with a survey of various therapy used and discarded in the field of allergy, followed by Clarence S. Livingood, M.D., speaking on the comparative toxicity of various drugs used in therapy. Herman Blatt, M.D., Associate ACA, demonstrated new work in the field of bacteriology, and Charles B. Shuey presented a discussion of urticaria and its problems.

At a luncheon, November 6, Dr. Stanley Hampton summarized ACTH and cortisone as used in allergic problems. Later C. M. Pomerat, M.D., showed a movie representing three years of observations on responses of human allergic cells in tissue culture; and John M. Sheldon, M.D., spoke on the practical management of asthma. A special presentation was a round table on the subject of bacteria and its role in the field of allergy, organized by Drs. L. O. Dutton, Oscar Swineford, and Clement Sullivan.

AMERICAN MEDICAL WRITERS' ASSOCIATION

Dr. Lewis J. Moorman, of Oklahoma City, Secretary of the Oklahoma State Medical Association, Editor of the *Journal of the Oklahoma State Medical Association,* and former Dean and Professor of Medicine, University of Oklahoma School of Medicine, was elected President-Elect of the American Medical Writers' Association at the eighth annual meeting held in Peoria, Illinois, on September 19. The other officers elected were Dr. Jacob E. Reisch of Springfield, Illinois, First Vice President; Dr. J. Spencer Felton of Oak Ridge, Tennessee, Second Vice President; Dr. Harold Swanberg of Quincy, Illinois, Secretary-Treasurer (re-elected); Dr. Lee D. Van Antwerp of Chicago, Editor; Dr. Norbert C. Barwasser of Moline, Illinois, Accounting Officer. Those elected members of the Board of Directors were Dr. John R. Miner, Rochester, Minnesota; Dr. Wallace Marshall, Two Rivers, Wisconsin; Dr. Everett M. George, Des Moines, Iowa; Dr. Norris J. Heckel, Chicago; Dr. Theodore R. Van Dellen, Chicago; Dr. C. W. Schumacher, St. Louis; Dr. M. Pierce Rucker, Richmond, Virginia; and Miss Helen Penn, St. Louis.

The new president, elected last year, is Dr. Arkell M. Vaughn of Chicago, Associate Professor of Surgery, Loyola University, and the retiring president is Dr. Julius Jensen of St. Louis, formerly of Washington University.

The Association has been incorporated not-for-profit in Illinois, and a new constitution was adopted at Peoria which somewhat liberalizes membership for non-medical persons but does not lower the educational requirements. The 1952 meeting will be held at the Jefferson Hotel, St. Louis, October 1, during the 17th annual meeting of the Mississippi Valley Medical Society.

AMERCAN ACADEMY OF DERMATOLOGY AND SYPHILOLOGY

The tenth annual meeting of the American Academy of Dermatology and Syphilology was held in Chicago at the Palmer House, December 8-13. In addition to the special courses in x-ray and radium, bacteriology of the skin, anatomy and embryology of the skin, and special problems in dermatohistopathology held at the Palmer House, special courses in histopathology and mycology were held at the medical schools of the University of Illinois and Northwestern University. Extensive scientific and technical exhibits as well as thirty-six informal discussion groups were features of the meeting.

Among the interesting lectures presented were "Bacterial Infections of the Skin"

by Dr. Donald M. Pillsbury; "Recent Experience in the Use of Cortisone with ACTH" by Dr. Rachmiel Levine; "The Present Status of Research in Cancer" by Dr. C. P. Rhoads; "The Clinical Significance of Disturbances in Sweat Delivery" by Dr. Marion B. Sulzberger; and "Newer Knowledge of Pituitary-Adrenal Physiology" by Dr. Jerome W. Conn.

ACA MEMBER REQUESTS SURVEY

Julio Cueva Celazquez, M.D., Associate Fellow of the College, residing in Mexico, requests all allergists who are making investigations of atmospheric pollens in the city in which they live, to send him a report of their findings. Dr. Cueva intends to write a paper comparing incidence of pollens in other cities with that in cities of Mexico. Such information will be valuable to physicians in Mexico who can send their allergic patients to areas free of specific pollens.

Correspondence should be addressed to: Dr. Julio Cueva Celazquez, Monterrey Street 101, Mexico City, Mexico, D.F.

NEWS ABOUT ACA MEMBERS

Merle Moore, M.D., F.A.C.A., has been appointed Head of the Department of Allergy, Medical School, University of Oregon. Doctor Moore is Associate Professor of Medicine; he was formerly a member of the Board of Regents of The American College of Allergists.

CLINICAL NOTES

Thos. Leeming & Co., Inc., announces availability of Nephenalin, a radically different antiasthmatic agent, combining in a single tablet elements that dilate the bronchi in about ninety seconds and extend this initial asthma relief four hours or more.

The thin outer coating of the Nephenalin tablet contains 10 mg. of N-isopropyl arterenol, epinephrine precursor and potent bronchodilator that is rapidly effective through sublingual absorption but of relatively brief action. The nucleus of the Nephenalin tablet, swallowed after the arterenol coating has provided quick relief of asthmatic symptoms, contains the reliable, long-acting antiasthmatic combination of theophylline, 2 grs., ephedrine sulfate, ⅜ grs., and phenobarbital, ⅛ gr. Thus Nephenalin combines two tested, highly effective antiasthmatic agents in a single tablet: the prompt, ninety-second relief obtained from the arterenol coating is relayed and sustained four hours by the long-acting nuclear ingredients.

Asthma patients may thus control their symptoms all day with only three Nephenalin tablets. This new form of therapy is as simple and convenient to use as it is clinically effective. A single tablet provides exceptionally rapid and prolonged relief. Extensive clinical research by leading allergists is now under way. Nephenalin is available from Thos. Leeming & Co., Inc., 155 East 44th Street, New York 17, N. Y.

* * *

Hollister-Stier Laboratories, manufacturers of pollen and protein extracts and advisers to physicians in allergenic problems for thirty years, have opened a fourth laboratory in Chicago for Midwest patrons. Other plants are located in Wilkinsburg, Pennsylvania; Spokane, Washington; and Los Angeles, California. The new laboratory, located at 127 North Dearborn Street, Chicago 2, Illinois, will give faster and better service for the center of the country.

BOOK REVIEWS

1951 CURRENT THERAPY. By Howard F. Conn, Ed. 699 pages. Price $10.00. Philadelphia: W. B. Saunders Company, 1951.

This third, or 1951, issue makes available up to the minute the latest improved methods for the treatment of disease. The ultimate aim of the physician is either to cure or alleviate suffering; in most illnesses these aims coincide. Therefore, specific as well as symptomatic agents must be considered in the management of all diseases. Therapy is presented by a list of 275 contributors, nationally recognized authorities on their subjects. Sound therapy must be based upon an accurate diagnosis and the use of effective therapeutic agents. The knowledge and experience of teachers and research workers must be in a practical, usable form to be of value to the practicing physician. Contributors to 1951 Current Therapy have been carefully selected because of their active interest in the specific disease discussed and because of their eminence in the medical world. Present methods of treatment are presented in succinct discussions devoid of irrelevant material. Diagnosis is given only when it is an integral part of therapy.

In the latest volume, forty-nine new contributors have been added and eighty-six of the methods are new; many of the articles have been significantly changed. There is necessarily some repetition from previous volumes when radical changes in therapy have not taken place, but the physician is interested to know when the therapy has not been changed or improved. More than one method may be given by different authorities, but in each case it represents the opinion of a recognized physician.

There are sixteen sections including diseases of infection, the respiratory system, cardiovascular system, blood and spleen, digestive tract, metabolism and nutrition, endocrine system, urogenital tract, allergy, skin, nervous system, and gynecologic conditions. The publishers are to be congratulated on the excellent format of the book.

DIFFERENTIAL DIAGNOSIS OF INTERNAL DISEASES. By Julius Bauer, M.D. 866 pages, 56 figures. Price $12.00. New York: Grune & Stratton, 1950.

This book is undoubtedly one of the few authoritative volumes on differential diagnosis of internal diseases. All physicians are prone at times to make a snap diagnosis. This book should be a control which will do much to make for a proper and accurate diagnosis. The tendency to use antibiotics indiscriminately or to perform blood transfusions before the nature of the anemia has been studied is well known. By such precocious therapy, harm may be done. Differential diagnosis requires thoroughness in observation and examination of the patient, knowledge, experience, shrewdness. It is true that differential diagnosis may be limited in scope, but mistakes must not be made by missing a disease that is curable by specific therapy based on elimination measures.

The 866 pages are divided into two parts: Part I, which contains twelve chapters, deals with leading symptoms; Part II has eight chapters on leading signs. Pain involving various domains of the body is adequately discussed. This is followed by disorders of general feelings and of consciousness, and by a discussion of vertigo, nausea, paralysis, inco-ordination, cough, diarrhea and constipation, and hemorrhages. The chapter on the habitus of the patient is very thorough. The diagnosis of diseases

involving hyperthermia, fever, infectious diseases, and of the respiratory, cardiovascular, digestive, hemopoietic, and uropoietic systems is complete. There is an accurate author and subject index.

The binding of the book is very durable, and the publishers are to be congratulated on their photographs.

POLLINOSIS—Clinical and Botanical Study (Polinosis—Estudio Clinico y Botanico). By Plutarco Naranjo V., M.D. 220 pages. Quito, Ecuador: Imp. de la Universidad Central, 1950.

Any study of one of the major factors in respiratory allergies which gives detailed information concerning various parts of the world is most welcome. The author reports a very conscientious survey of pollens producing hay fever in Ecuador and also gives a brief review of the diagnosis, prognosis, and treatment of hay fever. The first part consists of three chapters: basic concepts of allergy, classification of allergic diseases, and pollinosis. There follows a section on history, etiology, and symptomatology of pollinosis. Special chapters deal with hay fever and asthma. The second part deals with pollens and spores. There is a chapter on the atmospheric pollens and spores at Quito and the allergenic flora of Ecuador. The appendix contains lists of the allergenic flora of Mexico, Puerto Rico, Cuba, Colombia, Peru, Argentina, Uruguay, Brazil, and Venezuela.

The author is to be congratulated for including so much practical knowledge in compact form.

The book is printed in Spanish.

PRINCIPI DI ALLERGIA CLINICA. By Piero Sangiorgi, Docente of Pathology and Special Medicine, University of Milan. With a Foreword by Cesare Frugoni, Director of the General Medical Clinic, University of Rome. 493 pages, 59 figures. Price 3500 lira. Milan: Societa Editrice P.A., 1951.

It is to be regretted that there is no English translation of this fine book written in Italian by one of the foremost European allergists. There are five sections containing thirty chapters. The appendix contains both an authors' index and an analytical index, as well as an alphabetical list of allergens. Following a historical review, there is a complete chapter on the classification and terminology of allergic diseases; chapters appear on anaphylaxis, clinical allergy, various factors influencing allergy, the characteristics of allergy, constitutional factors, predisposing factors toward allergy, and the histology, physiology, and anatomic pathology of allergy. All chapters are followed by a concise bibliography. The third section deals with the general and specific diagnosis of allergy. Section 4 deals with symptomatic therapy, the important allergenic factors, specific desensitization, nonspecific desensitization, and the treatment of predisposing factors. Part 5 treats of allergies of the various domains of the body.

The illustrations are good, the print is readable. Since this volume is practical and a good textbook for the student of allergy as well as the allergist, it is hoped that an English translation will appear soon.

Index to Advertisers

Index to Volume 9

AUTHOR AND SUBJECT INDEX

A

B

C

D

E

F

G

H

I

M

N

O

P

Q

R

S

T

U

V

W

Y

Z

BOOK REVIEWS

EDITORIAL

EDITOR'S PAGE

IN MEMORIAM

NEWS ITEMS

PROGRESS IN ALLERGY

ANNALS of ALLERGY

PUBLISHED BY THE AMERICAN COLLEGE OF ALLERGISTS

Graduate Instructional Course—April 4-6, 1952

and

Eighth Annual Congress—April 7-9, 1952

Hotel William Penn, Pittsburgh

November-December
1951

lume 9, Number 6 **Published Bimonthly**

NNUAL SUBSCRIPTION $6.00 **SINGLE COPIES $1.50**

Prelude to asthma?

not necessarily...

Tedral, taken at first sign of attack, often forestalls severe symptoms.

in 15 minutes...Tedral brings symptomatic relief with a definite increase in vital capacity. Breathing becomes easier as Tedral relaxes smooth muscle, reduces tissue edema, provides mild sedation.

for 4 full hours...Tedral maintains more normal respiration for a sustained period—not just a momentary pause in the attack.

Prompt and prolonged relief with Tedral can be initiated any time, day or night, whenever needed without fear of incapacitating side effects.

Tedral provides:

theophylline	2 gr.
ephedrine	3/8 gr.
phenobarbital	1/8 gr.

in boxes of 24, 120 and 1000 tablets

Tedral

CHILCOTT *Laboratories* DIVISION OF The Maltine Company MORRIS PLAINS, NEW JERSEY